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(54) Title: METHODS FOR THE DIAGNOSIS, PROGNOSIS AND TREATMENT OF GLAUCOMA AND RELATED DISORDERS

(57) Abstract

The nucleic acid upstream of the TIGR protein encoding sequence can be used to diagnose glaucoma. Polymorphisms, base substitutions, base additions located with the upstream and within TIGR exons can also be used to diagnose glaucoma. In addition, polymorphisms, base substitutions, base additions located with the upstream and within TIGR exons can also be used to prognose glaucoma.

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5 **TITLE OF THE INVENTION:**

**METHODS FOR THE DIAGNOSIS, PROGNOSIS AND TREATMENT OF
GLAUCOMA AND RELATED DISORDERS**

10

FIELD OF THE INVENTION:

The present invention is in the fields of diagnostics, prognosis, and treatment, and concerns methods and reagents for diagnosing and treating glaucoma and related disorders.

15 **BACKGROUND OF THE INVENTION:**

"Glaucomas" are a group of debilitating eye diseases that are the leading cause of preventable blindness in the United States and other developed nations. Primary Open Angle Glaucoma ("POAG") is the most common form of glaucoma. The disease is characterized by the alteration of the trabecular meshwork, leading to 20 obstruction of the normal ability of aqueous humor to leave the eye without closure of the space (e.g., the "angle") between the iris and cornea (see, Vaughan, D. *et al.*, In: *General Ophthalmology*, Appleton & Lange, Norwalk, CT, pp. 213-230 (1992)). A characteristic of such obstruction in this disease is an increased intraocular pressure ("IOP"), resulting in progressive visual loss and blindness if not treated 25 appropriately and in a timely fashion.

The disease is estimated to affect between 0.4% and 3.3% of all adults over 40 years old (Leske, M.C. *et al.*, *Amer. J. Epidemiol.* 113:1843-1846 (1986); Bengtsson, B., *Br. J. Ophthalmol.* 73:483-487 (1989); Strong, N.P., *Ophthal. Physiol. Opt.* 12:3-7 (1992)). Moreover, the prevalence of the disease rises with age to over 6% of those 75 years 30 or older (Strong, N.P., *Ophthal. Physiol. Opt.* 12:3-7 (1992)).

A link between the IOP response of patients to glucocorticoids and the disease of POAG has long been suspected. While only 5% of the normal population shows a high IOP increase (16 mm Hg) to topical glucocorticoid testing, greater than 40-50% of patients with POAG show this response. In addition, an Open Angle glaucoma may be induced by exposure to glucocorticoids. This observation has suggested that an increased or abnormal glucocorticoid response in trabecular cells may be involved in POAG (Zhan, G.L. et al., *Exper. Eye Res.* 54:211-218 (1992); Yun, A.J. et al., *Invest. Ophthalmol. Vis. Sci.* 30:2012-2022 (1989); Clark, A.F., *Exper. Eye Res.* 55:265 (1992); Klemetti, A., *Acta Ophthalmol.* 68:29-33 (1990); Knepper, P.A., U.S. Patent No. 4,617,299). The ability of glucocorticoids to induce a glaucoma-like condition has led to efforts to identify genes or gene products that would be induced by the cells of the trabecular meshwork in response to glucocorticoids (Polansky, J.R. et al., In: *Glaucoma Update IV*, Springer-Verlag, Berlin, pp. 20-29 (1991)). Initial efforts using short-term exposure to dexamethasone revealed only changes in specific protein synthesis. Extended exposure to relatively high levels of dexamethasone was, however, found to induce the expression of related 66 kD and 55 kD proteins that could be visualized by gel electrophoresis (Polansky, J.R. et al., In: *Glaucoma Update IV*, Springer-Verlag, Berlin, pp. 20-29 (1991)). The induction kinetics of these proteins as well as their dose response characteristics were similar to the kinetics that were required for steroid-induced IOP elevation in human subjects (Polansky, J.R. et al., In: *Glaucoma Update IV*, Springer-Verlag, Berlin, pp. 20-29 (1991)). Problems of aggregation and apparent instability or loss of protein in the purification process were obstacles in obtaining a direct protein sequence.

Because increased IOP is a readily measurable characteristic of glaucoma, the diagnosis of the disease is largely screened for by measuring intraocular pressure (tonometry) (Strong, N.P., *Ophthal. Physiol. Opt.* 12:3-7 (1992), Greve, M. et al., *Can. J. Ophthalmol.* 28:201-206 (1993)). Unfortunately, because glaucomatous and normal pressure ranges overlap, such methods are of limited value unless multiple readings are obtained (Hitchings, R.A., *Br. J. Ophthalmol.* 77:326 (1993); Tuck, M.W. et al., *Ophthal. Physiol. Opt.* 13:227-232 (1993); Vaughan, D. et al., In: *General Ophthalmology*, Appleton & Lange, Norwalk, CT, pp. 213-230 (1992); Vernon, S.A., *Eye* 7:134-137 (1993)). For this reason, additional methods, such as direct examination of the optic disk and determination of the extent of a patient's visual field loss are often conducted to improve the accuracy of diagnosis (Greve, M. et al., *Can. J. Ophthalmol.* 28:201- 206 (1993)). Moreover, these techniques are of limited prognostic value.

Nguyen *et al.*, U.S. Patent Application No: 08/649,432 filed May 17, 1996, the entire disclosure of which is hereby incorporated by reference as if set forth at length herein, disclosed a novel protein sequence highly induced by glucocorticoids in the endothelial lining cells of the human trabecular meshwork. Nguyen *et al.*, U.S.

- 5 Patent Application No: 08/649,432 also disclosed the cDNA sequence for that protein, the protein itself, molecules that bind to it, and nucleic acid molecules that encode it, and provided improved methods and reagents for diagnosing glaucoma and related disorders, as well as for diagnosing other diseases or conditions, such as cardiovascular, immunological, or other diseases or conditions that affect the
10 expression or activity of the protein.

The present invention provides improved diagnostic agents, prognostic agents, therapeutic agents and methods.

SUMMARY OF THE INVENTION:

- 15 An object of the invention is to provide a method for diagnosing glaucoma in a patient which comprises the steps: (A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that specifically hybridizes to a polynucleotide that is linked to a TIGR promoter, and a
20 complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule, and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting TIGR response in said patient; (B) permitting hybridization between said
25 marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and (C) detecting the presence of said polymorphism, wherein the detection of the polymorphism is diagnostic of glaucoma.

- Another object of the invention is to provide a method for prognosing glaucoma in a patient which comprises the steps: (A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that specifically hybridizes to a polynucleotide that is linked to a TIGR promoter, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid

molecule, and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting TIGR response in said patient; (B) permitting hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and (C) detecting the presence of said polymorphism, wherein the detection of the polymorphism is prognostic of glaucoma.

Another object of the invention is to provide marker nucleic acid molecules capable of specifically detecting *TIGRmt1*, *TIGRmt2*, *TIGRmt3*, *TIGRmt4*, *TIGRmt5* and *TIGRsv1*.

Another object of the invention is to provide a method for diagnosing steroid sensitivity in a patient which comprises the steps: (A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, the marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that is linked to a TIGR promoter, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of the patient, wherein nucleic acid hybridization between the marker nucleic acid molecule, and the complementary nucleic acid molecule obtained from the patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting TIGR response in the patient; (B) permitting hybridization between said TIGR-encoding marker nucleic acid molecule and the complementary nucleic acid molecule obtained from the patient; and (C) detecting the presence of the polymorphism, wherein the detection of the polymorphism is diagnostic of steroid sensitivity.

Further objects of the invention provide a nucleic acid molecule that comprises the sequence of SEQ ID NO: 1, recombinant DNA molecules containing a polynucleotide that specifically hybridizes to SEQ ID NO: 1 and substantially purified molecules that specifically bind to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 1.

Further objects of the invention provide a nucleic acid molecule that comprises the sequence of SEQ ID NO: 3, recombinant DNA molecules containing a polynucleotide that specifically hybridizes to SEQ ID NO: 3 and substantially purified molecules that specifically bind to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 3.

Additional objects of the invention provide a nucleic acid molecule that comprises the sequence of SEQ ID NO: 4, recombinant DNA molecules containing a polynucleotide that specifically hybridizes to SEQ ID NO: 4 and substantially

purified molecules that specifically bind to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 4.

Additional objects of the invention provide a nucleic acid molecule that comprises the sequence of SEQ ID NO: 5, recombinant DNA molecules containing a polynucleotide that specifically hybridizes to SEQ ID NO: 5 and substantially purified molecules that specifically bind to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 5.

An additional object of the present invention is to provide a method of treating glaucoma which comprises administering to a glaucomatous patient an effective amount of an agent that inhibits the synthesis of a TIGR protein.

Indeed, the molecules of the present invention may be used to diagnose diseases or conditions which are characterized by alterations in the expression of extracellular proteins.

BRIEF DESCRIPTION OF THE FIGURES:

Figures 1A, 1B, 1C, 1D and 1E provide the nucleic acid sequence of a TIGR promoter region (SEQ ID NO: 1) from an individual without glaucoma.

Figures 2A, 2B, 2C and 2D provide the location and sequence changes highlighted in bold associated with glaucoma mutants *TIGRmt1*, *TIGRmt2*, *TIGRmt3*, *TIGRmt4*, *TIGRmt5*, and *TIGRsv1* (SEQ ID NO: 2).

Figures 3A, 3B, 3C, 3D, 3E, 3F, and 3G provide nucleic acid sequences of a TIGR promoter, and TIGR exons, TIGR introns and TIGR downstream sequences (SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5).

Figure 4 provides a diagrammatic representation of the location of primers on the TIGR gene promoter for Single Strand Conformational Polymorphism (SSCP) analysis.

Figure 5 provides a diagrammatic representation of the TIGR exons and the arrangement of SSCP primers.

Figure 6 provides a homology analysis of TIGR homology with olfactomedin and olfactomedin-related proteins.

Figure 7 shows the nucleotide sequence of TIGR (SEQ ID NO: 26).

Figure 8 shows the amino acid sequence of TIGR (SEQ ID NO: 32).

DETAILED DESCRIPTION OF THE INVENTION:

I. Agents of the Invention

As used herein, the term "glaucoma" has its art recognized meaning, and includes both primary glaucomas, secondary glaucomas, juvenile glaucomas, congenital glaucomas, and familial glaucomas, including, without limitation, pigmentary glaucoma, high tension glaucoma and low tension glaucoma and their related diseases. The methods of the present invention are particularly relevant to the diagnosis of POAG, OAG, juvenile glaucoma, and inherited glaucomas. The methods of the present invention are also particularly relevant to the prognosis of POAG, OAG, juvenile glaucoma, and inherited glaucomas. A disease or condition is said to be related to glaucoma if it possesses or exhibits a symptom of glaucoma, for example, an increased intra-ocular pressure resulting from aqueous outflow resistance (see, Vaughan, D. et al., In: *General Ophthalmology*, Appleton & Lange, Norwalk, CT, pp. 213-230 (1992)). The preferred agents of the present invention are discussed in detail below.

The agents of the present invention are capable of being used to diagnose the presence or severity of glaucoma and its related diseases in a patient suffering from glaucoma (a "glaucomatous patient"). The agents of the present invention are also capable of being used to prognose the presence or severity of glaucoma and its related diseases in a person not yet suffering from any clinical manifestations of glaucoma. Such agents may be either naturally occurring or non-naturally occurring. As used herein, a naturally occurring molecule may be "substantially purified," if desired, such that one or more molecules that is or may be present in a naturally occurring preparation containing that molecule will have been removed or will be present at a lower concentration than that at which it would normally be found.

The agents of the present invention will preferably be "biologically active" with respect to either a structural attribute, such as the capacity of a nucleic acid to hybridize to another nucleic acid molecule, or the ability of a protein to be bound by antibody (or to compete with another molecule for such binding). Alternatively, such an attribute may be catalytic, and thus involve the capacity of the agent to mediate a chemical reaction or response.

As used herein, the term "TIGR protein" refers to a protein having the amino acid sequence of SEQ ID NO: 32. As used herein, the agents of the present invention comprise nucleic acid molecules, proteins, and organic molecules.

As indicated above, the trabecular meshwork has been proposed to play an important role in the normal flow of the aqueous, and has been presumed to be the

major site of outflow resistance in glaucomatous eyes. Human trabecular meshwork (HTM) cells are endothelial like cells which line the outflow channels by which aqueous humor exits the eye; altered synthetic function of the cells may be involved in the pathogenesis of steroid glaucoma and other types of glaucoma. Sustained 5 steroid treatment of these cells are interesting because it showed that a major difference was observed when compared to 1-2 day glucocorticoid (GC) exposure. This difference appears relevant to the clinical onset of steroid glaucoma (1-6 weeks).

Although trabecular meshwork cells had been found to induce specific 10 proteins in response to glucocorticoids (see, Polansky, J.R., In: "Basic Aspects of Glaucoma Research III", Schattauer, New York 307-318 (1993)), efforts to purify the expressed protein were encumbered by insolubility and other problems. Nguyen, T.D. et al., (In: "Basic Aspects of Glaucoma Research III", Schattauer, New York, 331-343 15 (1993), herein incorporated by reference) used a molecular cloning approach to isolate a highly induced mRNA species from glucocorticoid-induced human trabecular cells. The mRNA exhibited a time course of induction that was similar to the glucocorticoid-induced proteins. The clone was designated "II.2" (ATCC No: 97994, American Type Culture Collection, Rockville Maryland).

Nguyen et al., U.S. Patent Application No: 08/649,432 filed May 17, 1996, 20 isolated a II.2 clone which encoded a novel secretory protein that is induced in cells of the trabecular meshwork upon exposure to glucocorticoids. It has been proposed that this protein may become deposited in the extracellular spaces of the trabecular meshwork and bind to the surface of the endothelial cells that line the trabecular meshwork, thus causing a decrease in aqueous flow. Quantitative dot blot analysis 25 and PCR evaluations have shown that the mRNA exhibits a progressive induction with time whereas other known GC-inductions from other systems and found in HTM cells (metallothionein, alpha-1 acid glycoprotein and alpha-1 antichymotrypsin) reached maximum level at one day or earlier. Of particular interest, the induction level of this clone was very high (4-6% total cellular mRNA) 30 with control levels undetectable without PCR method. Based on studies of ^{35}S methionine cell labeling, the clone has the characteristics recently discovered for the major GC-induced extracellular glycoprotein in these cells, which is a sialenated, N-glycosylated molecule with a putative inositol phosphate anchor. The induction of mRNA approached 4% of the total cellular mRNA. The mRNA increased 35 progressively over 10 days of dexamethasone treatment. The II.2 clone is 2.0 Kb

whereas the Northern blotting shows a band of 2.5 Kb. Although not including a poly A tail, the 3' end of the clone contains two consensus polyadenylation signals.

A genomic clone was isolated and designated P₁TIGR clone (ATCC No: 97570, American Type Culture Collection, Rockville, Maryland). In-situ hybridization using the P₁TIGR clone shows a TIGR gene and/or a sequence or sequences that specifically hybridize to the TIGR gene located at chromosome 1, q21-27, and more preferably to the TIGR gene located at chromosome 1, q22-26, and most preferably to the TIGR gene located at chromosome 1, q24. Clone P₁TIGR comprises human genomic sequences that specifically hybridize to the TIGR gene cloned into the BamHI site of vector pCYPAC (Ioannou *et al.*, *Nature Genetics*, 6:84-89 (1994) herein incorporated by reference).

As used herein, the term "TIGR gene" refers to the region of DNA involved in producing a TIGR protein; it includes, without limitation, regions preceding and following the coding region as well as intervening sequences between individual coding regions.

As used herein, the term "TIGR exon" refers to any interrupted region of the TIGR gene that serves as a template for a mature TIGR mRNA molecule. As used herein, the term "TIGR intron" refers to a region of the TIGR gene which is non-coding and serves as a template for a TIGR mRNA molecule.

Localization studies using a Stanford G3 radiation hybrid panel mapped the TIGR gene near the D1S2536 marker with a LOD score of 6.0 (Richard *et al.*, *American Journal of Human Genetics* 52.5: 915-921 (1993), herein incorporated by reference); Frazer *et al.*, *Genomics* 14.3: 574-578 (1992), herein incorporated by reference; Research Genetics, Huntsville, Alabama). Other markers in this region include: D1S210; D1S1552; D1S2536; D1S2790; SHGC-12820; and D1S2558.

Sequences located upstream of the TIGR coding region are isolated and sequenced in a non-glaucomic individual. The upstream sequence is set forth in SEQ ID No. 1. Sequence comparisons of the upstream region of a non-glaucoma individual and individuals with glaucoma identify a number of mutations in individuals with glaucoma. These mutations are illustrated in Figure 2. Five mutations are identified. *TIGRmt1* is the result of a replacement of a cytosine with a guanine at position 4337 (SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3). *TIGRmt2* is the result of a replacement of a cytosine with a thymine at position 4950 (SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3). *TIGRmt3* is the result of an addition in the following order of a guanine, a thymine, a guanine, and a thymine

(GTGT) at position 4998 (SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3). *TIGRmt4* is the result of a replacement of an adenine with a guanine at position 4256 (SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3). *TIGRmt5* is the result of a replacement of a guanine with an adenine at position 4262 (SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3). One or more of *TIGRmt1*, *TIGRmt2*, *TIGRmt3*, *TIGRmt4*, and *TIGRmt5* can be homozygous or heterozygous.

Sequence comparisons of the upstream region of a non-glaucoma individual and individuals with glaucoma identify at least one sequence variation in individuals with glaucoma. One such sequence variant is illustrated in Figure 2. 10 *TIGRsv1* is the result of a replacement of an adenine with a guanine at position 4406 (SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3).

Molecules comprising sequences upstream of the TIGR coding region provide useful markers for polymorphic studies. Such molecules include primers suitable for single strand conformational polymorphic studies, examples of which 15 are as follows: forward primer "Sk-1a": 5'-TGA GGC TTC CTC TGG AAA C-3' (SEQ ID NO: 6); reverse primer "ca2": 5'-TGA AAT CAG CAC ACC AGT AG-3' (SEQ ID NO: 7); forward primer "CA2": 5'-GCA CCC ATA CCC CAA TAA TAG-3' (SEQ ID NO: 8); reverse primer "Pr+1": 5'-AGA GTT CCC CAG ATT TCA CC-3' (SEQ ID NO: 9); forward primer "Pr-1": 5'-ATC TGG GGA ACT CTT CTC AG-3' (SEQ ID 20 NO: 10); reverse primer "Pr+2(4A2)": 5'-TAC AGT TGT TGC AGA TAC G-3' (SEQ ID NO: 11); forward primer "Pr-2(4A)": 5'-ACA ACG TAT CTG CAA CAA CTG-3' (SEQ ID NO: 12); reverse primer "Pr+3(4A)": 5'-TCA GGC TTA ACT GCA GAA CC-3' (SEQ ID NO: 13); forward primer "Pr-3(4A)": 5'-TTG GTT CTG CAG TTA AGC C-3' (SEQ ID NO: 14); reverse primer "Pr+2(4A1)": 5'-AGC AGC ACA AGG 25 GCA ATC C-3' (SEQ ID NO: 15); reverse primer "Pr+1(4A)": 5'-ACA GGG CTA TAT TGT GGG-3' (SEQ ID NO: 16).

In addition, molecules comprising sequences within TIGR exons provide useful markers for polymorphic studies. Such molecules include primers suitable for single strand conformational polymorphic studies, examples of which are as 30 follows: forward primer "KS1X": 5'-CCT GAG ATG CCA GCT GTC C-3' (SEQ ID NO: 17); reverse primer "SK1XX": 5'-CTG AAG CAT TAG AAG CCA AC-3' (SEQ ID NO: 18); forward primer "KS2a1": 5'-ACC TTG GAC CAG GCT GCC AG-3' (SEQ ID NO: 19); reverse primer "SK3": 5'-AGG TTT GTT CGA GTT CCA G-3' (SEQ ID NO: 20); forward primer "KS4": 5'-ACA ATT ACT GGC AAG TAT GG-3' (SEQ 35 ID NO: 21); reverse primer "SK6A": 5'-CCT TCT CAG CCT TGC TAC C-3' (SEQ ID

NO: 22); forward primer "KS5": 5'-ACA CCT CAG CAG ATG CTA CC-3' (SEQ ID NO: 23); reverse primer "SK8": 5'-ATG GAT GAC TGA CAT GGC C-3' (SEQ ID NO: 24); forward primer "KS6": 5'-AAG GAT GAA CAT GGT CAC C-3' (SEQ ID NO: 25).

5 The locations of primers: Sk-1a, ca2, CA2, Pr+1, Pr-1, Pr+2(4A2), Pr-2(4A),
Pr+3(4A), Pr-3(4A), Pr-3(4A), Pr+2(4A1), and Pr+1(4A) are diagrammatically set forth
in Figure 4. The location of primers: KS1X, SK1XX, Ks2a1, SK3, KS4, SK6A, KS5,
SK8, and KS6 are diagrammatically set forth in Figure 5.

10 The primary structure of the TIGR coding region initiates from an ATG initiation site (SEQ ID NO: 3, residues 5337-5339) and includes a 20 amino acid consensus signal sequence a second ATG (SEQ ID NO: 3, residues 5379-5381), indicating that the protein is a secretory protein. The nucleotide sequence for the TIGR coding region is depicted in Figure 7 (SEQ ID NO: 26). The protein contains
15 an N-linked glycosylation site located in the most hydrophilic region of the molecule. The amino terminal portion of the protein is highly polarized and adopts alpha helical structure as shown by its hydropathy profile and the Garnier-Robison structure analysis. In contrast, the protein contains a 25 amino acid hydrophobic region near its carboxy terminus. This region may comprise a glucocorticoid-induced protein (GIP) anchoring sequence. The amino acid sequence of TIGR is
20 depicted in Figure 8 (SEQ ID NO: 33).

25 Study of cyclohexamide treatment in the absence and presence of GC suggest that the induction of TIGR may involve factors in addition to the GC receptor. The TIGR gene may be involved in the cellular stress response since it is also induced by stimulants such as H₂O₂, 12-O-tetradecanoylphorbol-13-acetate (TPA), and high glucose; this fact may relate to glaucoma pathogenesis and treatment.

Sequence comparison of the upstream region identify a number of DNA motifs (*cis* elements). These DNA motifs or *cis* elements are shown in Figure 1. These motifs include, without limitation, glucocorticoid response motif(s), shear stress response motif(s), NFκB recognition motif(s), and AP1 motif(s). The locations 30 of these and other motifs are diagrammatically set forth in Figure 1. As used herein, the term "*cis* elements capable of binding" refers to the ability of one or more of the described *cis* elements to specifically bind an agent. Such binding may be by any chemical, physical or biological interaction between the *cis* element and the agent, including, but not limited, to any covalent, steric, agostic, electronic and ionic 35 interaction between the *cis* element and the agent. As used herein, the term

"specifically binds" refers to the ability of the agent to bind to a specified *cis* element but not to wholly unrelated nucleic acid sequences.

A preferred class of agents comprises TIGR nucleic acid molecules ("TIGR molecules"). Such molecules may be either DNA or RNA. A second preferred class 5 of agents ("TIGR molecules") comprises the TIGR protein, its peptide fragments, fusion proteins, and analogs.

Expression of the rat PRL gene is highly restricted to pituitary lactotroph cells and is induced by the cAMP-dependent protein kinase A pathway. At least one of the redundant pituitary specific elements (PRL-FP111) of the proximal rat PRL 10 promotor is required for this protein kinase A effect (Rajnarayan *et al.*, *Molecular Endocrinology* 4: 502-512 (1995), herein incorporated by reference). A sequence corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 is set forth in Figure 1 at residues 370-388 and 4491-4502, respectively. In accordance 15 with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of molecules that bind the PRL-FP111 upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

20 A consensus sequence (GR/PR), recognized by both the glucocorticoid receptor of rat liver and the progesterone receptor from rabbit uterus, has been reported to be involved in glucocorticoid and progesterone-dependent gene expression (Von der Ahe *et al.*, *Nature* 313: 706-709 (1985), herein incorporated by reference). A sequence corresponding to a GC/PR upstream motif or *cis* element is 25 set forth in Figure 1 at residues 433-445. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of glucocorticoid or progesterone or their homologues, including, but not limited to, the concentration of 30 glucocorticoid or progesterone or their homologues bound to an GC/PR upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

Shear stress motif (SSRE) or *cis* element has been identified in a number of 35 genes including platelet-derived growth factor B chain, tissue plasminogen activator

(tPA), ICAM-1 and TGF- β 1 (Resnick *et al.*, *Proc. Natl. Acad. Sci. (USA)* 80: 4591-4595 (1993), herein incorporated by reference). Transcription of these genes has been associated with humoral stimuli such as cytokines and bacterial products as well as hemodynamic stress forces. Sequences corresponding to a upstream shear stress motif or *cis* element are set forth in Figure 1 at residues 446-451, 1288-1293, 3597-3602, 4771-4776, and 5240-5245, respectively. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of molecules capable of binding the shear stress motif. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A consensus sequence for a glucocorticoid response upstream motif (GRE) or *cis* element has been characterized (Beato, *Cell* 56: 335-344 (1989); Becker *et al.*, *Nature* 324: 686-688 (1986), herein incorporated by reference; Sakai *et al.*, *Genes and Development* 2: 1144-1154 (1988), herein incorporated by reference). Genes containing this upstream motif or *cis* element are regulated by glucocorticoids, progesterone, androgens and mineral corticoids (Beato, *Cell* 56: 335-344 (1989)). Sequences corresponding to glucocorticoid response upstream motif or *cis* element are set forth in Figure 1 at residues 574-600, 1042-1056, 2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-4614, 4851-4865, 4844-4864, 5079-5084, and 5083-5111, respectively. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of molecules capable of binding a glucocorticoid response upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A sequence specific binding site (CBE) for the wild type nuclear phosphoprotein, p53, has been identified and appears to be associated with replication origins (Kern *et al.* *Science* 252: 1708-1711 (1991), herein incorporated by reference). A sequence corresponding to an CBE upstream motif or *cis* element is set forth in Figure 1 at residues 735-746. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of p53 or its homologues,

including, but not limited to, the concentration of p53 or its homologues bound to an CBE upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used
5 in the treatment of glaucoma.

Nuclear factor ets-like (NFE), a transcriptional activator that facilitates p50 and c-Rel-dependent IgH 3' enhancer activity has been shown to bind to an NFE site in the Rel-dependent IgH 3' enhancer (Linderson *et al.*, *European J. Immunology* 27: 468-475 (1997), herein incorporated by reference). A sequence corresponding to an
10 NFE upstream motif or *cis* element is set forth in Figure 1 at residues 774-795. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to,
15 the concentration of nuclear factors or their homologues bound to an NFE upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

An upstream motif or *cis* element (KTF.1-CS) for a control element 3' to the
20 human keratin 1 gene that regulates cell type and differentiation-specific expression has been identified (Huff *et al.*, *J. Biological Chemistry* 268: 377-384 (1993), herein incorporated by reference). A sequence corresponding to an upstream motif or *cis* element characteristic of KTF.1-CS is set forth in Figure 1 at residues 843-854. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or
25 concentration of KTF.1-CS or its homologues, including, but not limited to, the concentration of KTF.1-CS or its homologues bound to a KTF.1-CS upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of
30 glaucoma.

A progesterone responsive element (PRE) that maps to the far upstream steroid dependent DNase hypersensitive site of chicken lysozyme chromatin has been characterized (Hecht *et al.*, *EMBO J.* 7: 2063-2073 (1988), herein incorporated by
35 reference). The element confers hormonal regulation to a heterologous promoter

and is composed of a cluster of progesterone receptor binding sites. A sequence corresponding to an upstream motif or *cis* element characteristic of PRE is set forth in Figure 1 at residues 987-1026. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of molecules capable of binding a progesterone responsive PRE upstream motif or *cis* element. Such agents may be useful in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A sequence (ETF-EGFR) has been characterized which serves as a motif for a *trans*-active transcription factor that regulates expression of the epidermal growth factor receptor (Regec *et al.*, *Blood* 85:2711-2719 (1995), herein incorporated by reference). A sequence corresponding to an ETF-EGFR upstream motif or *cis* element is set forth in Figure 1 at residues 1373-1388. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the concentration of nuclear factors or their homologues bound to an ETF-EGFR upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A common trans-acting factor (SRE-cFos) has been shown to regulate skeletal and cardiac alpha-Actin gene transcription in muscle (Muscat *et al.*, *Molecular and Cellular Biology* 10: 4120-4133 (1988), herein incorporated by reference). A sequence corresponding to an SRE-cFos upstream motif or *cis* element is set forth in Figure 1 at residues 1447-1456. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the concentration of nuclear factors or their homologues bound to an SRE-cFos upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

Alu repetitive elements are unique to primates and are interspersed within the human genome with an average spacing of 4Kb. While some Alu sequences are actively transcribed by polymerase III, normal transcripts may also contain Alu-derived sequences in 5' or 3' untranslated regions (Jurka and Mikahanjia, *J. Mol.*

5 *Evolution* 32: 105-121 (1991), herein incorporated by reference, Claveria and Makalowski, *Nature* 371: 751-752 (1994), herein incorporated by reference). A sequence corresponding to an Alu upstream motif or *cis* element is set forth in Figure 1 at residues 1331-1550. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of 10 altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the concentration of nuclear factors or their homologues bound to an Alu upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such 15 agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A consensus sequence for a vitellogenin gene-binding protein (VBP) upstream motif or *cis* element has been characterized (Iyer *et al.*, *Molecular and Cellular Biology* 11: 4863-4875 (1991), herein incorporated by reference). Expression of the VBP gene commences early in liver ontogeny and is not subject to circadian 20 control. A sequence corresponding to an upstream motif or *cis* element capable of binding VBP is set forth in Figure 1 at residues 1786-1797. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of VBP or its homologues, including, but not limited to, the concentration of VBP or its 25 homologues bound to an VBP upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A structural motif (Malt-CS) or *cis* element involved in the activation of all 30 promoters of the maltose operons in *Escherichia coli* and *Klebsiella pneumoniae* has been characterized (Vidal-Inigliardi *et al.*, *J. Mol. Biol.* 218: 323-334 (1991), herein incorporated by reference). A sequence corresponding to a upstream Malt-CS motif or *cis* element is set forth in Figure 1 at residues 1832-1841. In accordance with the 35 embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of

molecules capable of binding the upstream Malt-CS motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

- 5 A consensus sequence for an estrogen receptor upstream motif or *cis* element has been characterized (ERE) (Forman *et al.*, *Mol. Endocrinology* 4: 1293-1301 (1990), herein incorporated by reference; de Verneuil *et al.*, *Nucleic Acid Res.* 18: 4489-4497 (1990), herein incorporated by reference; Gaub *et al.*, *Cell* 63: 1267-1276 (1990), herein incorporated by reference. A sequence corresponding to half an upstream motif or *cis* element capable of binding estrogen receptor is set forth in Figure 1 at residues 10 2166-2195, 3413-3429, and 3892-3896, respectively. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration, of the estrogen receptor or its homologues bound to an upstream motif or *cis* element.
- 15 Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

- Certain protein-binding sites (NF-mutagen) in Ig gene enhancers which determine transcriptional activity and inducibility have been shown to interact with 20 nuclear factors (Lenardo *et al.*, *Science* 236: 1573-1577 (1987), herein incorporated by reference). A sequence corresponding to an NF-mutagen upstream motif or *cis* element is set forth in Figure 1 at residues 2329-2338. In accordance with the 25 embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the concentration of nuclear factors or their homologues bound to an NF-mutagen upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of 30 glaucoma.

- A consensus sequence for a transcriptional repressor of c-myc (myc-PRF) upstream motif or *cis* element has been identified (Kakkis *et al.*, *Nature* 339: 718-719 35 (1989), herein incorporated by reference). Myc-PRF interacts with another widely distributed protein, myc-CF1 (common factor 1), which binds nearby and this association may be important in myc-PRF repression. A sequence corresponding to

an upstream motif or *cis* element capable of binding myc-PRF is set forth in Figure 1 at residues 2403-2416. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of myc-PRF or its homologues, 5 including, but not limited to, the concentration of myc-PRF or its homologues bound to an myc-PRF upstream motif or *cis* element Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

10 Human transcription factor activator protein 2 (AP2) is a transcription factor that has been shown to bind to Sp1, nuclear factor 1 (NF1) and simian virus 40 transplantation (SV40 T) antigen binding sites. It is developmentally regulated (Williams and Tijan, *Gene Dev.* 5: 670-682 (1991), herein incorporated by reference; Mitchell *et al.*, *Genes Dev.* 5: 105-119 (1991), herein incorporated by reference; Couto 15 *et al.*, *Nucleic Acid Research* 18: 57-64 (1990), herein incorporated by reference; Comb *et al.*, *Nucleic Acid Research* 18: 3975-3982 (1990), herein incorporated by reference; Winings *et al.*, *Nucleic Acid Research* 19: 3709-3714 (1991), herein incorporated by reference). Sequences corresponding to an upstream motif or *cis* element capable of binding AP2 are set forth in Figure 1 at residues 2520-2535, and 5170-5187, 20 respectively. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of AP2 or its homologues, including, but not limited to, the concentration of AP2 or its homologues bound to an upstream motif or *cis* element. Such agents may be useful in the study of glaucoma 25 pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

30 Drosophila RNA polymerase II heat shock transcription factor (HSTF) is a transcription factor that has been shown to be required for active transcription of an hsp 70 gene (Parker and Topol, *Cell* 37: 273-283 (1984), herein incorporated by reference). Sequences corresponding to an upstream motif or *cis* element capable of binding HSTF are set forth in Figure 1 at residues 2622-2635, and 5105-5132. In accordance with the embodiments of the present invention, transcription of TIGR 35 molecules can be effected by agents capable of altering the biochemical properties or concentration of HSTF or its homologues, including, but not limited to, the

concentration of HSTF or its homologues bound to an HSTF upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of 5 glaucoma.

A sequence corresponding to an upstream motif or *cis* element characteristic of SBF is set forth in Figure 1 at residues 2733-2743 (Shore *et al.*, *EMBO J.* 6: 461-467 (1987), herein incorporated by reference). In accordance with the embodiments of 10 the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of molecules that bind the SBF upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

An NF1 motif or *cis* element has been identified which recognizes a family of 15 at least six proteins (Courtois, *et al.*, *Nucleic Acid Res.* 18: 57-64 (1990), herein incorporated by reference; Mul *et al.*, *J. Virol.* 64: 5510-5518 (1990), herein incorporated by reference; Rossi *et al.*, *Cell* 52: 405-414 (1988), herein incorporated by reference; Gounari *et al.*, *EMBO J.* 10: 559-566 (1990), herein incorporated by 20 reference; Goyal *et al.*, *Mol. Cell Biol.* 10: 1041-1048 (1990); herein incorporated by reference; Mermond *et al.*, *Nature* 332: 557-561 (1988), herein incorporated by reference; Gronostajski *et al.*, *Molecular and Cellular Biology* 5: 964-971 (1985), herein incorporated by reference; Hennighausen *et al.*, *EMBO J.* 5: 1367-1371 (1986), herein incorporated by reference; Chodosh *et al.*, *Cell* 53: 11-24 (1988), herein incorporated by 25 reference). The NF1 protein will bind to an NF1 motif or *cis* element either as a dimer (if the motif is palindromic) or as a single molecule (if the motif is not palindromic). The NF1 protein is induced by TGF β (Faisst and Meyer, *Nucleic Acid Research* 20: 3-26 (1992), herein incorporated by reference). Sequences corresponding 30 to an upstream motif or *cis* element capable of binding NF1 are set forth in Figure 1 at residues 2923-2938, 4143-4167, and 4886-4900, respectively. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of NF1 or its homologues, including, but not limited to, the concentration of NF1 or its homologues bound to an upstream motif or *cis* element. Such agents can be used in 35 the study of glaucoma pathogenesis. In another embodiment, such agents can also

be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

Conserved regulatory sequences (NF-MHCIIA/B) of a rabbit major histocompatibility complex (MHC) class II gene are responsible for binding two distinct nuclear factors NF-MHCIIA and NF-MHCIIB and are believed to be involved in the regulation of coordinate expression of the class II genes – eg. MHC class II gene in B lymphocytes (*Sittisombut Molecular and Cellular Biology* 5: 2034-2041 (1988), herein incorporated by reference). A sequence corresponding to an NF-MHCIIA/B upstream motif or *cis* element is set forth in Figure 1 at residues 2936-2944. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of NF-MHCIIA or NF-MHCIIB or their homologues, including, but not limited to, the concentration of NF-MHCIIA or NF-MHCIIB or their homologues bound to an NF-MHCIIA/B upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

PEA 1 binding motifs or *cis* elements have been identified (Piette and Yaniv, *EMBO J.* 5: 1331-1337 (1987), herein incorporated by reference). The PEA1 protein is a transcription factor that is reported to bind to both the polyoma virus and c-fos enhancers. A sequence corresponding to an upstream motif or *cis* element capable of binding PEA1 is set forth in Figure 1 at residues 3285-3298. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of PEA1 or its homologues, including, but not limited to, the concentration of PEA1 or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A conserved *cis*-acting regulatory element (ICS) has been shown to bind trans-acting constitutive nuclear factors present in lymphocytes and fibroblasts which are involved in the interferon (IFN)-mediated transcriptional enhancement of MHC class-I and other genes (Shirayoshi *et al.*, *Proc. Natl. Acad. Sci. (USA)* 85: 5884-5888 (1988), herein incorporated by reference). A sequence corresponding to an ICS upstream motif or *cis* element is set forth in Figure 1 at residues 3688-3699. In

accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the concentration of nuclear factors or their homologues bound to an ICS upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A consensus sequence for an ISGF2 upstream motif or *cis* element has been characterized (Iman *et al.*, *Nucleic Acids Res.* 18: 6573-6580 (1990), herein incorporated by reference; Harada *et al.*, *Cell* 63: 303-312 (1990), herein incorporated by reference; Yu-Lee *et al.*, *Mol. Cell Biol.* 10: 3087-3094 (1990), herein incorporated by reference; Pine *et al.*, *Mol. Cell Biol.* 10: 32448-2457 (1990), herein incorporated by reference). ISGF2 is induced by interferon α and γ , prolactin and virus infections. A sequence corresponding to an upstream motif or *cis* element capable of binding ISGF2 is set forth in Figure 1 at residues 4170-4179. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of ISGF2 or its homologues, including, but not limited to, the concentration of ISGF2 or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A sequence corresponding to an upstream motif or *cis* element capable of binding zinc is set forth in Figure 1 at residues 4285-4292. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of zinc. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

A sequence corresponding to an upstream motif or *cis* element characteristic of CAP/CRP-galO is set forth in Figure 1 at residues 4379-4404 (Taniguchi *et al.*, *Proc. Natl. Acad. Sci (USA)* 76: 5090-5094 (1979), herein incorporated by reference). In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or

concentration of molecules that bind the CAP/CRP-galO upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of 5 glaucoma.

Human transcription factor activator protein 1 (AP1) is a transcription factor that has been shown to regulate genes which are highly expressed in transformed cells such as stromelysin, *c-fos*, α_1 -anti-trypsin and collagenase (Gutman and Wasylyk, *EMBO J.* 9:7: 2241-2246 (1990), herein incorporated by reference; Martin *et al.*, *Proc. Natl. Acad. Sci. USA* 85: 5839-5843 (1988), herein incorporated by reference; 10 Jones *et al.*, *Genes and Development* 2: 267-281 (1988), herein incorporated by reference; Faisst and Meyer, *Nucleic Acid Research* 20: 3-26 (1992), herein incorporated by reference; Kim *et al.*, *Molecular and Cellular Biology* 10: 1492-1497 (1990), herein incorporated by reference; Baumhueter *et al.*, *EMBO J.* 7: 2485-2493 15 (1988), herein incorporated by reference). The AP1 transcription factor has been associated with genes that are activated by 12-O-tetradecanoylphorbol-13-acetate (TPA) (Gutman and Wasylyk, *EMBO J.* 7: 2241-2246 (1990)). Sequences corresponding to an upstream motif or *cis* element capable of binding AP1 are set forth in Figure 1 at residues 4428-4434 and 4627-4639, respectively. In accordance 20 with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of AP1 or its homologues, including, but not limited to, the concentration of AP1 or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can 25 also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

The sex-determining region of the Y chromosome gene, *sry*, is expressed in the fetal mouse for a brief period, just prior to testis differentiation. SRY is a DNA binding protein known to bind to a CACA-rich region in the *sry* gene (Vriz *et al.*, 30 *Biochemistry and Molecular Biology International* 37: 1137-1146 (1995), herein incorporated by reference). A sequence corresponding to an upstream motif or *cis* element capable of binding SRY is set forth in Figure 1 at residues 4625-4634. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or 35 concentration of SRY or its homologues, including, but not limited to, the

concentration of SRY or its homologues bound to an upstream motif or *cis* element. Such agents may be useful in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

5 A sequence corresponding to an upstream motif or *cis* element characteristic of GC2-GH is set forth in Figure 1 at residues 4689-4711 (West *et al.*, *Molecular and Cellular Biology* 7: 1193-1197 (1987), herein incorporated by reference). In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or
10 concentration of GC2-GH or its homologues, including, but not limited to, the concentration of GC2-GH or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of
15 glaucoma.

PEA 3 binding motifs or *cis* elements have been identified (Martin *et al.*, *Proc. Natl. Acad. Sci. (USA)* 85: 5839-5843 (1988), herein incorporated by reference; Gutman and Wasylyk, *EMBO J.* 7: 2241-2246 (1990), herein incorporated by reference). The PEA3 protein is a transcription factor that is reported to interact
20 with AP1 like proteins (Martin *et al.*, *Proc. Natl. Acad. Sci. (USA)* 85: 5839-5843 (1988), herein incorporated by reference). Sequences corresponding to an upstream motif or *cis* element capable of binding PEA3 is set forth in Figure 1 at residues 4765-4769. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or
25 concentration of PEA3 or its homologues, including, but not limited to, the concentration of PEA3 or its homologues bound to an upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

30 Mammalian interspersed repetitive (MIR) is an element involved in the coding and processing sequences of mammalian genes. The MIR element is at least 260 bp in length and numbers about 10^5 copies within the mammalian genome (Murnane *et al.*, *Nucleic Acids Research* 15: 2837-2839 (1995), herein incorporated by reference). A sequence corresponding to an MIR upstream motif or *cis* element is set forth in Figure 1 at residues 4759-4954. In accordance with the embodiments of
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the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of nuclear factors or their homologues, including, but not limited to, the concentration of nuclear factors or their homologues bound to an MIR upstream motif or *cis* element. Such agents 5 can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

Normal liver and differentiated hepatoma cell lines contain a hepatocyte-specific nuclear factor (HNF-1) which binds *cis*-acting element sequences within the 10 promoters of the alpha and beta chains of fibrinogen and alpha 1-antitrypsin (Baumhueter *et al.*, *EMBO J.* 8: 2485-2493, herein incorporated by reference). A sequence corresponding to an HNF-1 upstream motif or *cis* element is set forth in Figure 1 at residues 4923-4941. In accordance with the embodiments of the present 15 invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of HNF-1 or its homologues, including, but not limited to, the concentration of HNF-1 or its homologues bound to an HNF-1 upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used 20 in the treatment of glaucoma.

A number of *cis* elements or upstream motifs have been associated with gene regulation by steroid and thyroid hormones (e.g. glucocorticoid and estrogen)(Beato, *Cell* 56: 335-344 (1989), herein incorporated by reference; Brent *et al.*, *Molecular Endocrinology* 89:1996-2000 (1989), herein incorporated by reference; Glass 25 *et al.*, *Cell* 54: 313-323 (1988), herein incorporated by reference; Evans, *Science* 240: 889-895 (1988), herein incorporated by reference).

A consensus sequence for a thyroid receptor upstream motif or *cis* element (TRE) has been characterized (Beato, *Cell* 56: 335-344 (1989), herein incorporated by 30 reference). A sequence corresponding to a thyroid receptor upstream motif or *cis* element is set forth in Figure 1 at residues 5151-5156. Thyroid hormones are capable of regulating genes containing a thyroid receptor upstream motif or *cis* element (Glass *et al.*, *Cell* 54: 313-323 (1988), herein incorporated by reference). Thyroid hormones can negatively regulate TIGR. In accordance with the 35 embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of

molecules capable of binding a thyroid receptor upstream motif or *cis* element. Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

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NF κ B is a transcription factor that is reportedly associated with a number of biological processes including T-cell activation and cytokine regulation (Lenardo *et al.*, *Cell* 58: 227-229 (1989), herein incorporated by reference). A consensus upstream motif or *cis* element capable of binding NF κ B has been reported (Lenardo *et al.*, *Cell* 58: 227-229 (1989)). Sequences corresponding to an upstream motif or *cis* element capable of binding NF κ B are set forth in Figure 1 at residues 5166-5175. In accordance with the embodiments of the present invention, transcription of TIGR molecules can be effected by agents capable of altering the biochemical properties or concentration of NF κ B or its homologues, including, but not limited to, the concentration of NF κ B or its homologues bound to an upstream motif or *cis* element.

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Such agents can be used in the study of glaucoma pathogenesis. In another embodiment, such agents can also be used in the study of glaucoma prognosis. In another embodiment such agents can be used in the treatment of glaucoma.

Where one or more of the agents is a nucleic acid molecule, such nucleic acid molecule may be sense, antisense or triplex oligonucleotides corresponding to any part of the TIGR promoter, TIGR cDNA, TIGR intron, TIGR exon or TIGR gene.

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The TIGR promoter, or fragment thereof, of the present invention may be cloned into a suitable vector and utilized to promote the expression of a marker gene (e.g. firefly luciferase (de Wet, *Mol. Cell Biol.* 7: 725-737 (1987), herein incorporated by reference) or GUS (Jefferson *et al.*, *EMBO J.* 6: 3901-3907 (1987), herein incorporated by reference)). In another embodiment of the present invention, a TIGR promoter may be cloned into a suitable vector and utilized to promote the expression of a TIGR gene in a suitable eukaryotic or prokaryotic host cell (e.g. human trabecular cell, chinese hamster cell, *E. coli*). In another embodiment of the present invention, a TIGR promoter may be cloned into a suitable vector and utilized to promote the expression of a homologous or heterologous gene in a suitable eukaryotic or prokaryotic host cells (e.g. human trabecular cell lines, chinese hamster cells, *E. coli*).

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Practitioners are familiar with the standard resource materials which describe specific conditions and procedures for the construction, manipulation and isolation of macromolecules (e.g., DNA molecules, plasmids, etc.), generation of recombinant

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organisms and the screening and isolating of clones, (see for example, Sambrook *et al.*, In *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press (1989), herein incorporated by reference in its entirety; Old and Primrose, In *Principles of Gene Manipulation: An Introduction To Genetic Engineering*, Blackwell (1994),
5 herein incorporated by reference).

The TIGR promoter or any portion thereof of the present invention may be used in a gel-retardation or band shift assay (Old and Primrose, In *Principles of Gene Manipulation: An Introduction To Genetic Engineering*, Blackwell (1994)). Any of the *cis* elements identified in the present invention may be used in a gel-retardation or band shift assay to isolate proteins capable of binding the *cis* element.
10 Suitable DNA fragments or molecules comprise or consist of one or more of the following: sequences corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 as set forth in Figure 1 at residues 370-388, and 4491-4502, respectively, a sequence corresponding to an upstream motif or *cis* element
15 capable of binding GR/PR as set forth in Figure 1 at residues 433-445, sequences corresponding to an upstream shear stress motif or *cis* element as set forth in Figure 1 at residues 446-451, 1288-1293, 3597-3602, 4771-4776, and 5240-5245, respectively,
20 sequences corresponding to glucocorticoid response upstream motif or *cis* element as set forth in Figure 1 at residues 574-600, 1042-1056, 2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-4614, 4851-4865, 4844-4864, 5079-5084, 5083-5111, respectively,
25 a sequence corresponding to an upstream motif or *cis* element capable of binding CBE as set forth in Figure 1 at residues 735-746, a sequence corresponding to an upstream motif or *cis* element capable of binding NFE as set forth in Figure 1 at residues 774-795, a sequence corresponding to an upstream motif or *cis* element
30 capable of binding KTF.1-CS as set forth in Figure 1 at residues 843-854, a sequence corresponding to an upstream motif or *cis* element capable of binding PRE is set forth in Figure 1 at residues 987-1026, a sequence corresponding to an upstream motif or *cis* element capable of binding ETF-EGFR as set forth in Figure 1 at residues 1373-1388, a sequence corresponding to an upstream motif or *cis* element
35 capable of binding SRE-cFos as set forth in Figure 1 at residues 1447-1456, a sequence corresponding to an upstream motif or *cis* element capable of binding Alu as set forth in Figure 1 at residues 1331-1550, a sequence corresponding to an upstream motif or *cis* element capable of binding VBP as set forth in Figure 1 at residues 1786-1797, a sequence corresponding to an upstream motif or *cis* element capable of binding Malt-CS as set forth in Figure 1 at residues 1832-1841, sequences

corresponding to an upstream motif or *cis* element capable of binding ERE as set forth in Figure 1 at residues 2167-2195, 3413-3429, and 3892-3896, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-mutagen as set forth in Figure 1 at residues 2329-2338, a sequence corresponding to
5 an upstream motif or *cis* element capable of binding myc-PRF as set forth in Figure 1 at residues 2403-2416, sequences corresponding to an upstream motif or *cis* element capable of binding AP2 as set forth in Figure 1 at residues 2520-2535 and 5170-5187, respectively, sequences corresponding to an upstream motif or *cis* element capable of binding HSTF as set forth in Figure 1 at residues 2622-2635, and
10 5105-5132, respectively, a sequence corresponding to an upstream motif or *cis* element characteristic of SBF as set forth in Figure 1 at residues 2733-2743, sequences corresponding to an upstream motif or *cis* element capable of binding NF-1 as set forth in Figure 1 at residues 2923-2938, 4144-4157, and 4887-4900, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-
15 MHCIIA/B as set forth in Figure 1 at residues 2936-2944, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA1 as set forth in Figure 1 at residues 3285-3298, a sequence corresponding to an upstream motif or *cis* element capable of binding ICS as set forth in Figure 1 at residues 3688-3699, a sequence corresponding to an upstream motif or *cis* element capable of binding
20 ISGF2 as set forth in Figure 1 at residues 4170-4179, a sequence corresponding to an upstream motif or *cis* element capable of binding zinc as set forth in Figure 1 at residues 4285-4293, a sequence corresponding to an upstream motif or *cis* element characteristic of CAP/CRP-galO as set forth in Figure 1 at residues 4379-4404, sequences corresponding to an upstream motif or *cis* element capable of binding
25 AP1 as set forth in Figure 1 at residues 4428-4434, and 4627-4639, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding SRY as set forth in Figure 1 at residues 4625-4634, a sequence corresponding to an upstream motif or *cis* element characteristic of GC2 as set forth in Figure 1 at residues 4678-4711, a sequence corresponding to an upstream motif or *cis* element
30 capable of binding PEA3 as set forth in Figure 1 at residues 4765-4769, a sequence corresponding to an upstream motif or *cis* element capable of MIR as set forth in Figure 1 at residues 4759-4954, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-HNF-1 as set forth in Figure 1 at residues 4923-4941, a sequence corresponding to a thyroid receptor upstream motif or *cis* element as set forth in Figure 1 at residues 5151-5156, and a sequence corresponding to an
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upstream motif or *cis* element capable of binding NF κ B as set forth in Figure 1 at residues 5166-5175.

A preferred class of agents of the present invention comprises nucleic acid molecules will encode all or a fragment of "TIGR promoter" or flanking gene sequences. As used herein, the terms "TIGR promoter" or "promoter" is used in an expansive sense to refer to the regulatory sequence(s) that control mRNA production. Such sequences include RNA polymerase binding sites, glucocorticoid response elements, enhancers, etc. All such TIGR molecules may be used to diagnose the presence of glaucoma and severity of glaucoma. Such molecules may 10 be either DNA or RNA.

Fragment nucleic acid molecules may encode significant portion(s) of, or indeed most of, SEQ ID NO: 1 or SEQ ID NO: 3 or SEQ ID NO: 4 or SEQ ID NO: 5. Alternatively, the fragments may comprise smaller oligonucleotides (having from about 15 to about 250 nucleotide residues, and more preferably, about 15 to about 30 15 nucleotide residues.). Such oligonucleotides include SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25.

Alternatively such oligonucleotides may derive from either the TIGR promoter, TIGR introns, TIGR exons, TIGR cDNA and TIGR downstream sequences comprise or consist of one or more of the following: sequences corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 as set forth in Figure 1 at residues 370-388, and 4491-4502, respectively, a sequence corresponding to an 20 upstream motif or *cis* element capable of binding GR/PR as set forth in Figure 1 at residues 433-445, sequences corresponding to an upstream shear stress motif or *cis* element as set forth in Figure 1 at residues 446-451, 1288-1293, 3597-3602, 4771-4776, 25 and 5240-5245, respectively, sequences corresponding to glucocorticoid response upstream motif or *cis* element as set forth in Figure 1 at residues 574-600, 1042-1056, 30 2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-4614, 4851-4865, 4844-4864, 5079-5084, 5083-5111, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding CBE as set forth in Figure 1 at residues 735-746, a sequence corresponding to an upstream motif or *cis* element capable of binding NFE as set forth in Figure 1 at residues 774-795, a sequence corresponding to an 35 upstream motif or *cis* element capable of binding KTF.1-CS as set forth in Figure 1

at residues 843-854, a sequence corresponding to an upstream motif or *cis* element capable of binding PRE is set forth in Figure 1 at residues 987-1026, a sequence corresponding to an upstream motif or *cis* element capable of binding ETF-EGFR as set forth in Figure 1 at residues 1373-1388, a sequence corresponding to an upstream motif or *cis* element capable of binding SRE-cFos as set forth in Figure 1 at residues 1447-1456, a sequence corresponding to an upstream motif or *cis* element capable of binding Alu as set forth in Figure 1 at residues 1331-1550, a sequence corresponding to an upstream motif or *cis* element capable of binding VBP as set forth in Figure 1 at residues 1786-1797, a sequence corresponding to an upstream motif or *cis* element capable of binding Malt-CS as set forth in Figure 1 at residues 1832-1841, sequences corresponding to an upstream motif or *cis* element capable of binding ERE as set forth in Figure 1 at residues 2167-2195, 3413-3429, and 3892-3896, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-mutagen as set forth in Figure 1 at residues 2329-2338, a sequence corresponding to an upstream motif or *cis* element capable of binding myc-PRF as set forth in Figure 1 at residues 2403-2416, sequences corresponding to an upstream motif or *cis* element capable of binding AP2 as set forth in Figure 1 at residues 2520-2535 and 5170-5187, respectively, sequences corresponding to an upstream motif or *cis* element capable of binding HSTF as set forth in Figure 1 at residues 2622-2635, and 5105-5132, respectively, a sequence corresponding to an upstream motif or *cis* element characteristic of SBF as set forth in Figure 1 at residues 2733-2743, sequences corresponding to an upstream motif or *cis* element capable of binding NF-1 as set forth in Figure 1 at residues 2923-2938, 4144-4157, and 4887-4900, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-MHCIIA/B as set forth in Figure 1 at residues 2936-2944, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA1 as set forth in Figure 1 at residues 3285-3298, a sequence corresponding to an upstream motif or *cis* element capable of binding ICS as set forth in Figure 1 at residues 3688-3699, a sequence corresponding to an upstream motif or *cis* element capable of binding ISGF2 as set forth in Figure 1 at residues 4170-4179, a sequence corresponding to an upstream motif or *cis* element capable of binding zinc as set forth in Figure 1 at residues 4285-4293, a sequence corresponding to an upstream motif or *cis* element characteristic of CAP/CRP-galO as set forth in Figure 1 at residues 4379-4404, sequences corresponding to an upstream motif or *cis* element capable of binding AP1 as set forth in Figure 1 at residues 4428-4434, and 4627-4639, respectively, a

sequence corresponding to an upstream motif or *cis* element capable of binding SRY as set forth in Figure 1 at residues 4625-4634, a sequence corresponding to an upstream motif or *cis* element characteristic of GC2 as set forth in Figure 1 at residues 4678-4711, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA3 as set forth in Figure 1 at residues 4765-4769, a sequence corresponding to an upstream motif or *cis* element capable of binding MIR as set forth in Figure 1 at residues 4759-4954, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-HNF-1 as set forth in Figure 1 at residues 4923-4941, a sequence corresponding to a thyroid receptor upstream motif or *cis* element as set forth in Figure 1 at residues 5151-5156, and a sequence corresponding to an upstream motif or *cis* element capable of binding NF κ B as set forth in Figure 1 at residues 5166-5175. For such purpose, the oligonucleotides must be capable of specifically hybridizing to a nucleic acid molecule genetically or physically linked to the TIGR gene. As used herein, the term "linked" refers to genetically, physically or operably linked.

As used herein, two nucleic acid molecules are said to be capable of specifically hybridizing to one another if the two molecules are capable of forming an anti-parallel, double-stranded nucleic acid structure, whereas they are unable to form a double-stranded structure when incubated with a non-TIGR nucleic acid molecule. A nucleic acid molecule is said to be the "complement" of another nucleic acid molecule if they exhibit complete complementarity. As used herein, molecules are said to exhibit "complete complementarity" when every nucleotide of one of the molecules is complementary to a nucleotide of the other. Two molecules are said to be "minimally complementary" if they can hybridize to one another with sufficient stability to permit them to remain annealed to one another under at least conventional "low-stringency" conditions. Similarly, the molecules are said to be "complementary" if they can hybridize to one another with sufficient stability to permit them to remain annealed to one another under conventional "high-stringency" conditions. Conventional stringency conditions are described by Sambrook, J., et al., (In: *Molecular Cloning, a Laboratory Manual*, 2nd Edition, Cold Spring Harbor Press, Cold Spring Harbor, New York (1989)), and by Haymes, B.D., et al. (In: *Nucleic Acid Hybridization, A Practical Approach*, IRL Press, Washington, DC (1985)), both herein incorporated by reference). Departures from complete complementarity are therefore permissible, as long as such departures do not completely preclude the capacity of the molecules to form a double-stranded

structure. Thus, in order for an oligonucleotide to serve as a primer it need only be sufficiently complementary in sequence to be able to form a stable double-stranded structure under the particular solvent and salt concentrations employed.

- Apart from their diagnostic or prognostic uses, such oligonucleotides may be
- 5 employed to obtain other TIGR nucleic acid molecules. Such molecules include the TIGR-encoding nucleic acid molecule of non-human animals (particularly, cats, monkeys, rodents and dogs), fragments thereof, as well as their promoters and flanking sequences. Such molecules can be readily obtained by using the above-described primers to screen cDNA or genomic libraries obtained from non-human
- 10 species. Methods for forming such libraries are well known in the art. Such analogs may differ in their nucleotide sequences from that of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18,
- 15 SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, or from molecules consisting of sequences corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 as set forth in Figure 1 at residues 370-388, and 4491-4502, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding GR/PR as set
- 20 forth in Figure 1 at residues 433-445, sequences corresponding to an upstream shear stress motif or *cis* element as set forth in Figure 1 at residues 446-451, 1288-1293, 3597-3602, 4771-4776, and 5240-5245, respectively, sequences corresponding to glucocorticoid response upstream motif or *cis* element as set forth in Figure 1 at residues 574-600, 1042-1056, 2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-4614,
- 25 4851-4865, 4844-4864, 5079-5084, 5083-5111, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding CBE as set forth in Figure 1 at residues 735-746, a sequence corresponding to an upstream motif or *cis* element capable of binding NFE as set forth in Figure 1 at residues 774-795, a sequence corresponding to an upstream motif or *cis* element capable of binding KTF.1-CS as
- 30 set forth in Figure 1 at residues 843-854, a sequence corresponding to an upstream motif or *cis* element capable of binding PRE is set forth in Figure 1 at residues 987-1026, a sequence corresponding to an upstream motif or *cis* element capable of binding ETF-EGFR as set forth in Figure 1 at residues 1373-1388, a sequence corresponding to an upstream motif or *cis* element capable of binding SRE-cFos as
- 35 set forth in Figure 1 at residues 1447-1456, a sequence corresponding to an upstream

motif or *cis* element capable of binding Alu as set forth in Figure 1 at residues 1331-1550, a sequence corresponding to an upstream motif or *cis* element capable of binding VBP as set forth in Figure 1 at residues 1786-1797, a sequence corresponding to an upstream motif or *cis* element capable of binding Malt-CS as set forth in Figure 1 at residues 1832-1841, sequences corresponding to an upstream motif or *cis* element capable of binding ERE as set forth in Figure 1 at residues 2167-2195, 3413-3429, and 3892-3896, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-mutagen as set forth in Figure 1 at residues 2329-2338, a sequence corresponding to an upstream motif or *cis* element capable of binding myc-PRF as set forth in Figure 1 at residues 2403-2416, sequences corresponding to an upstream motif or *cis* element capable of binding AP2 as set forth in Figure 1 at residues 2520-2535 and 5170-5187, respectively, sequences corresponding to an upstream motif or *cis* element capable of binding HSTF as set forth in Figure 1 at residues 2622-2635, and 5105-5132, respectively, a sequence corresponding to an upstream motif or *cis* element characteristic of SBF as set forth in Figure 1 at residues 2733-2743, sequences corresponding to an upstream motif or *cis* element capable of binding NF-1 as set forth in Figure 1 at residues 2923-2938, 4144-4157, and 4887-4900, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-MHCIIA/B as set forth in Figure 1 at residues 2936-2944, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA1 as set forth in Figure 1 at residues 3285-3298, a sequence corresponding to an upstream motif or *cis* element capable of binding ICS as set forth in Figure 1 at residues 3688-3699, a sequence corresponding to an upstream motif or *cis* element capable of binding ISGF2 as set forth in Figure 1 at residues 4170-4179, a sequence corresponding to an upstream motif or *cis* element capable of binding zinc as set forth in Figure 1 at residues 4285-4293, a sequence corresponding to an upstream motif or *cis* element characteristic of CAP/CRP-galO as set forth in Figure 1 at residues 4379-4404, sequences corresponding to an upstream motif or *cis* element capable of binding AP1 as set forth in Figure 1 at residues 4428-4434, and 4627-4639, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding SRY as set forth in Figure 1 at residues 4625-4634, a sequence corresponding to an upstream motif or *cis* element characteristic of GC2 as set forth in Figure 1 at residues 4678-4711, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA3 as set forth in Figure 1 at residues 4765-4769, a sequence corresponding to an upstream motif or *cis* element

capable of MIR as set forth in Figure 1 at residues 4759-4954, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-HNF-1 as set forth in Figure 1 at residues 4923-4941, a sequence corresponding to a thyroid receptor upstream motif or *cis* element as set forth in Figure 1 at residues 5151-5156,
5 and a sequence corresponding to an upstream motif or *cis* element capable of binding NF κ B as set forth in Figure 1 at residues 5166-5175 because complete complementarity is not needed for stable hybridization. The TIGR nucleic acid molecules of the present invention therefore also include molecules that, although
10 capable of specifically hybridizing with TIGR nucleic acid molecules may lack "complete complementarity."

Any of a variety of methods may be used to obtain the above-described nucleic acid molecules (Elles, Methods in Molecular Medicine: Molecular Diagnosis of Genetic Diseases, Humana Press (1996), herein incorporated by reference). SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6,
15 SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, sequences corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 as set forth in Figure 1
20 at residues 370-388, and 4491-4502, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding GR/PR as set forth in Figure 1 at residues 433-445, sequences corresponding to an upstream shear stress motif or *cis* element as set forth in Figure 1 at residues 446-451, 1288-1293, 3597-3602, 4771-4776,
25 and 5240-5245, respectively, sequences corresponding to glucocorticoid response upstream motif or *cis* element as set forth in Figure 1 at residues 574-600, 1042-1056,
2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-4614, 4851-4865, 4844-4864, 5079-
5084, 5083-5111, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding CBE as set forth in Figure 1 at residues 735-746, a
30 sequence corresponding to an upstream motif or *cis* element capable of binding NFE as set forth in Figure 1 at residues 774-795, a sequence corresponding to an upstream motif or *cis* element capable of binding KTF.1-CS as set forth in Figure 1 at residues 843-854, a sequence corresponding to an upstream motif or *cis* element capable of binding PRE as set forth in Figure 1 at residues 987-1026, a sequence corresponding to an upstream motif or *cis* element capable of binding ETF-EGFR as
35 set forth in Figure 1 at residues 1373-1388, a sequence corresponding to an upstream

motif or *cis* element capable of binding SRE-cFos as set forth in Figure 1 at residues 1447-1456, a sequence corresponding to an upstream motif or *cis* element capable of binding Alu as set forth in Figure 1 at residues 1331-1550, a sequence corresponding to an upstream motif or *cis* element capable of binding VBP as set forth in Figure 1 at residues 1786-1797, a sequence corresponding to an upstream motif or *cis* element capable of binding Malt-CS as set forth in Figure 1 at residues 1832-1841, sequences corresponding to an upstream motif or *cis* element capable of binding ERE as set forth in Figure 1 at residues 2167-2195, 3413-3429, and 3892-3896, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-mutagen as set forth in Figure 1 at residues 2329-2338, a sequence corresponding to an upstream motif or *cis* element capable of binding myc-PRF as set forth in Figure 1 at residues 2403-2416, sequences corresponding to an upstream motif or *cis* element capable of binding AP2 as set forth in Figure 1 at residues 2520-2535 and 5170-5187, respectively, sequences corresponding to an upstream motif or *cis* element capable of binding HSTF as set forth in Figure 1 at residues 2622-2635, and 5105-5132, respectively, a sequence corresponding to an upstream motif or *cis* element characteristic of SBF as set forth in Figure 1 at residues 2733-2743, sequences corresponding to an upstream motif or *cis* element capable of binding NF-1 as set forth in Figure 1 at residues 2923-2938, 4144-4157, and 4887-4900, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-MHCIIA/B as set forth in Figure 1 at residues 2936-2944, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA1 as set forth in Figure 1 at residues 3285-3298, a sequence corresponding to an upstream motif or *cis* element capable of binding ICS as set forth in Figure 1 at residues 3688-3699, a sequence corresponding to an upstream motif or *cis* element capable of binding ISGF2 as set forth in Figure 1 at residues 4170-4179, a sequence corresponding to an upstream motif or *cis* element capable of binding zinc as set forth in Figure 1 at residues 4285-4293, a sequence corresponding to an upstream motif or *cis* element characteristic of CAP/CRP-galO as set forth in Figure 1 at residues 4379-4404, sequences corresponding to an upstream motif or *cis* element capable of binding AP1 as set forth in Figure 1 at residues 4428-4434, and 4627-4639, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding SRY as set forth in Figure 1 at residues 4625-4634, a sequence corresponding to an upstream motif or *cis* element characteristic of GC2 as set forth in Figure 1 at residues 4678-4711, a sequence corresponding to an upstream motif or *cis* element

capable of binding PEA3 as set forth in Figure 1 at residues 4765-4769, a sequence corresponding to an upstream motif or *cis* element capable of MIR as set forth in Figure 1 at residues 4759-4954, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-HNF-1 as set forth in Figure 1 at residues 4923-4941,
5 a sequence corresponding to a thyroid receptor upstream motif or *cis* element as set forth in Figure 1 at residues 5151-5156, and a sequence corresponding to an upstream motif or *cis* element capable of binding NF κ B as set forth in Figure 1 at residues 5166-5175 may be used to synthesize all or any portion of the TIGR promoter or any of the TIGR upstream motifs or portions the TIGR cDNA
10 (Zamechik *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 83:4143 (1986); Goodchild *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 85:5507 (1988); Wickstrom *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 85:1028; Holt, J.T. *et al.*, *Molec. Cell. Biol.* 8:963 (1988); Gerwirtz, A.M. *et al.*, *Science* 242:1303 (1988); Anfossi, G., *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 86:3379 (1989); Becker, D., *et al.*, *EMBO J.* 8:3679 (1989); all of which references are incorporated
15 herein by reference).

Automated nucleic acid synthesizers may be employed for this purpose. In lieu of such synthesis, the disclosed SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, sequences corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 as set forth in Figure 1 at residues 370-388, and 4491-4502, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding GR/PR as set forth in Figure 1 at residues 433-445, sequences corresponding to an upstream shear stress motif or *cis* element as set forth in Figure 1 at residues 446-451, 1288-1293, 3597-3602, 4771-4776, and 5240-5245, respectively, sequences corresponding to glucocorticoid response upstream motif or *cis* element as set forth in Figure 1 at residues 574-600, 1042-1056, 2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-4614, 4851-4865, 4844-4864, 5079-5084, 5083-5111, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding CBE as set forth in Figure 1 at residues 735-746, a sequence corresponding to an upstream motif or *cis* element capable of binding NFE as set forth in Figure 1 at residues 774-795, a sequence corresponding to an upstream motif or *cis* element capable of binding KTF.1-CS as set forth in Figure 1 at residues 843-854, a sequence

corresponding to an upstream motif or *cis* element capable of binding PRE is set forth in Figure 1 at residues 987-1026, a sequence corresponding to an upstream motif or *cis* element capable of binding ETF-EGFR as set forth in Figure 1 at residues 1373-1388, a sequence corresponding to an upstream motif or *cis* element
5 capable of binding SRE-cFos as set forth in Figure 1 at residues 1447-1456, a sequence corresponding to an upstream motif or *cis* element capable of binding Alu as set forth in Figure 1 at residues 1331-1550, a sequence corresponding to an upstream motif or *cis* element capable of binding VBP as set forth in Figure 1 at residues 1786-1797, a sequence corresponding to an upstream motif or *cis* element
10 capable of binding Malt-CS as set forth in Figure 1 at residues 1832-1841, sequences corresponding to an upstream motif or *cis* element capable of binding ERE as set forth in Figure 1 at residues 2167-2195, 3413-3429, and 3892-3896, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-mutagen as set forth in Figure 1 at residues 2329-2338, a sequence corresponding to
15 an upstream motif or *cis* element capable of binding myc-PRF as set forth in Figure 1 at residues 2403-2416, sequences corresponding to an upstream motif or *cis* element capable of binding AP2 as set forth in Figure 1 at residues 2520-2535 and 5170-5187, respectively, sequences corresponding to an upstream motif or *cis* element capable of binding HSTF as set forth in Figure 1 at residues 2622-2635, and
20 5105-5132, respectively, a sequence corresponding to an upstream motif or *cis* element characteristic of SBF as set forth in Figure 1 at residues 2733-2743, sequences corresponding to an upstream motif or *cis* element capable of binding NF-1 as set forth in Figure 1 at residues 2923-2938, 4144-4157, and 4887-4900, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-
25 MHCIIA/B as set forth in Figure 1 at residues 2936-2944, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA1 as set forth in Figure 1 at residues 3285-3298, a sequence corresponding to an upstream motif or *cis* element capable of binding ICS as set forth in Figure 1 at residues 3688-3699, a sequence corresponding to an upstream motif or *cis* element capable of binding
30 ISGF2 as set forth in Figure 1 at residues 4170-4179, a sequence corresponding to an upstream motif or *cis* element capable of binding zinc as set forth in Figure 1 at residues 4285-4293, a sequence corresponding to an upstream motif or *cis* element characteristic of CAP/CRP-galO as set forth in Figure 1 at residues 4379-4404, sequences corresponding to an upstream motif or *cis* element capable of binding
35 AP1 as set forth in Figure 1 at residues 4428-4434, and 4627-4639, respectively, a

sequence corresponding to an upstream motif or *cis* element capable of binding SRY as set forth in Figure 1 at residues 4625-4634, a sequence corresponding to an upstream motif or *cis* element characteristic of GC2 as set forth in Figure 1 at residues 4678-4711, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA3 as set forth in Figure 1 at residues 4765-4769, a sequence corresponding to an upstream motif or *cis* element capable of MIR as set forth in Figure 1 at residues 4759-4954, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-HNF-1 as set forth in Figure 1 at residues 4923-4941, a sequence corresponding to a thyroid receptor upstream motif or *cis* element as set forth in Figure 1 at residues 5151-5156, and a sequence corresponding to an upstream motif or *cis* element capable of binding NF κ B as set forth in Figure 1 at residues 5166-5175 may be used to define a pair of primers that can be used with the polymerase chain reaction (Mullis, K. *et al.*, *Cold Spring Harbor Symp. Quant. Biol.* 51:263-273 (1986); Erlich H. *et al.*, EP 50,424; EP 84,796, EP 258,017, EP 237,362; Mullis, K., EP 201,184; Mullis K. *et al.*, US 4,683,202; Erlich, H., US 4,582,788; and Saiki, R. *et al.*, US 4,683,194)) to amplify and obtain any desired TIGR gene DNA molecule or fragment.

The TIGR promoter sequence(s) and TIGR flanking sequences can also be obtained by incubating oligonucleotide probes of TIGR oligonucleotides with members of genomic human libraries and recovering clones that hybridize to the probes. In a second embodiment, methods of "chromosome walking," or 3' or 5' RACE may be used (Frohman, M.A. *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 85:8998-9002 (1988), herein incorporated by reference); Ohara, O. *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 86:5673-5677 (1989), herein incorporated by reference) to obtain such sequences.

II. Uses of the Molecules of the Invention in the Diagnosis and Prognosis of Glaucoma and Related Diseases

A particularly desired use of the present invention relates to the diagnosis of glaucoma, POAG, pigmentary glaucoma, high tension glaucoma and low tension glaucoma and their related diseases. Another particularly desired use of the present invention relates to the prognosis of glaucoma, POAG, pigmentary glaucoma, high tension glaucoma and low tension glaucoma and their related diseases. As used herein the term "glaucoma" includes both primary glaucomas, secondary glaucomas, juvenile glaucomas, congenital glaucomas, and familial glaucomas,

including, without limitation, pigmentary glaucoma, high tension glaucoma and low tension glaucoma and their related diseases. As indicated above, methods for diagnosing or prognosing glaucoma suffer from inaccuracy, or require multiple examinations. The molecules of the present invention may be used to define
5 superior assays for glaucoma. Quite apart from such usage, the molecules of the present invention may be used to diagnosis or predict an individual's sensitivity to elevated intraocular pressure upon administration of steroids such as glucocorticoids or corticosteroids, or anti-inflammatory steroids). Dexamethasone, cortisol and prednisolone are preferred steroids for this purpose. Medical
10 conditions such as inflammatory and allergic disorders, as well as organ transplantation recipients, benefit from treatment with glucocorticoids. Certain individuals exhibit an increased sensitivity to such steroids (i.e., "steroid sensitivity"), which is manifested by an undesired increase in intraocular pressure.
15 The present invention may be employed to diagnosis or predict such sensitivity, as well as glaucoma and related diseases.

In a first embodiment, the TIGR molecules of the present invention are used to determine whether an individual has a mutation affecting the level (i.e., the concentration of TIGR mRNA or protein in a sample, etc.) or pattern (i.e., the kinetics of expression, rate of decomposition, stability profile, etc.) of the TIGR
20 expression (collectively, the "TIGR response" of a cell or bodily fluid) (for example, a mutation in the TIGR gene, or in a regulatory region(s) or other gene(s) that control or affect the expression of TIGR), and being predictive of individuals who would be predisposed to glaucoma (prognosis), related diseases, or steroid sensitivity. As used herein, the TIGR response manifested by a cell or bodily fluid is
25 said to be "altered" if it differs from the TIGR response of cells or of bodily fluids of normal individuals. Such alteration may be manifested by either abnormally increased or abnormally diminished TIGR response. To determine whether a TIGR response is altered, the TIGR response manifested by the cell or bodily fluid of the patient is compared with that of a similar cell sample (or bodily fluid sample) of
30 normal individuals. As will be appreciated, it is not necessary to re-determine the TIGR response of the cell sample (or bodily fluid sample) of normal individuals each time such a comparison is made; rather, the TIGR response of a particular individual may be compared with previously obtained values of normal individuals.

In one sub-embodiment, such an analysis is conducted by determining the
35 presence and/or identity of polymorphism(s) in the TIGR gene or its flanking

regions which are associated with glaucoma, or a predisposition (prognosis) to glaucoma, related diseases, or steroid sensitivity. As used herein, the term "TIGR flanking regions" refers to those regions which are located either upstream or downstream of the TIGR coding region.

- 5 Any of a variety of molecules can be used to identify such polymorphism(s). In one embodiment, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, 10 SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, sequences corresponding to an upstream motif or *cis* element characteristic of PRL-FP111 as set forth in Figure 1 at residues 370-388, and 4491-4502, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding GR/PR as set forth in Figure 1 at residues 433-445, sequences corresponding to an 15 upstream shear stress motif or *cis* element as set forth in Figure 1 at residues 446-451, 1288-1293, 3597-3602, 4771-4776, and 5240-5245, respectively, sequences corresponding to glucocorticoid response upstream motif or *cis* element as set forth in Figure 1 at residues 574-600, 1042-1056, 2444-2468, 2442-2269, 3536-3563, 4574-4593, 4595-4614, 4851-4865, 4844-4864, 5079-5084, 5083-5111, respectively, a sequence 20 corresponding to an upstream motif or *cis* element capable of binding CBE as set forth in Figure 1 at residues 735-746, a sequence corresponding to an upstream motif or *cis* element capable of binding NFE as set forth in Figure 1 at residues 774-795, a sequence corresponding to an upstream motif or *cis* element capable of binding KTF.1-CS as set forth in Figure 1 at residues 843-854, a sequence corresponding to an 25 upstream motif or *cis* element capable of binding PRE is set forth in Figure 1 at residues 987-1026, a sequence corresponding to an upstream motif or *cis* element capable of binding ETF-EGFR as set forth in Figure 1 at residues 1373-1388, a sequence corresponding to an upstream motif or *cis* element capable of binding SRE-cFos as set forth in Figure 1 at residues 1447-1456, a sequence corresponding to an 30 upstream motif or *cis* element capable of binding Alu as set forth in Figure 1 at residues 1331-1550, a sequence corresponding to an upstream motif or *cis* element capable of binding VBP as set forth in Figure 1 at residues 1786-1797, a sequence corresponding to an upstream motif or *cis* element capable of binding Malt-CS as set forth in Figure 1 at residues 1832-1841, sequences corresponding to an upstream 35 motif or *cis* element capable of binding ERE as set forth in Figure 1 at residues 2167-

2195, 3413-3429, and 3892-3896, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-mutagen as set forth in Figure 1 at residues 2329-2338, a sequence corresponding to an upstream motif or *cis* element capable of binding myc-PRF as set forth in Figure 1 at residues 2403-2416,
5 sequences corresponding to an upstream motif or *cis* element capable of binding AP2 as set forth in Figure 1 at residues 2520-2535 and 5170-5187, respectively, sequences corresponding to an upstream motif or *cis* element capable of binding HSTF as set forth in Figure 1 at residues 2622-2635, and 5105-5132, respectively, a sequence corresponding to an upstream motif or *cis* element characteristic of SBF as
10 set forth in Figure 1 at residues 2733-2743, sequences corresponding to an upstream motif or *cis* element capable of binding NF-1 as set forth in Figure 1 at residues 2923-2938, 4144-4157, and 4887-4900, respectively, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-MHCIIA/B as set forth in Figure 1 at residues 2936-2944, a sequence corresponding to an upstream motif or *cis*
15 element capable of binding PEA1 as set forth in Figure 1 at residues 3285-3298, a sequence corresponding to an upstream motif or *cis* element capable of binding ICS as set forth in Figure 1 at residues 3688-3699, a sequence corresponding to an upstream motif or *cis* element capable of binding ISGF2 as set forth in Figure 1 at residues 4170-4179, a sequence corresponding to an upstream motif or *cis* element
20 capable of binding zinc as set forth in Figure 1 at residues 4285-4293, a sequence corresponding to an upstream motif or *cis* element characteristic of CAP/CRP-galO as set forth in Figure 1 at residues 4379-4404, sequences corresponding to an upstream motif or *cis* element capable of binding AP1 as set forth in Figure 1 at residues 4428-4434, and 4627-4639, respectively, a sequence corresponding to an upstream
25 motif or *cis* element capable of binding SRY as set forth in Figure 1 at residues 4625-4634, a sequence corresponding to an upstream motif or *cis* element characteristic of GC2 as set forth in Figure 1 at residues 4678-4711, a sequence corresponding to an upstream motif or *cis* element capable of binding PEA3 as set forth in Figure 1 at residues 4765-4769, a sequence corresponding to an upstream
30 motif or *cis* element capable of MIR as set forth in Figure 1 at residues 4759-4954, a sequence corresponding to an upstream motif or *cis* element capable of binding NF-HNF-1 as set forth in Figure 1 at residues 4923-4941, a sequence corresponding to a thyroid receptor upstream motif or *cis* element as set forth in Figure 1 at residues 5151-5156, and a sequence corresponding to an upstream motif or *cis* element
35 capable of binding NFkB as set forth in Figure 1 at residues 5166-5175 (or a sub-

sequence thereof) may be employed as a marker nucleic acid molecule to identify such polymorphism(s).

Alternatively, such polymorphisms can be detected through the use of a marker nucleic acid molecule or a marker protein that is genetically linked to (i.e., a polynucleotide that co-segregates with) such polymorphism(s). As stated above, the TIGR gene and/or a sequence or sequences that specifically hybridize to the TIGR gene have been mapped to chromosome 1q, 21-32, and more preferably to the TIGR gene located at chromosome 1, q21-27, and more preferably to the TIGR gene located at chromosome 1, q22-26, and most preferably to the TIGR gene located at chromosome 1, q24. In a preferred aspect of this embodiment, such marker nucleic acid molecules will have the nucleotide sequence of a polynucleotide that is closely genetically linked to such polymorphism(s) (e.g., markers located at chromosome 1, q19-25 (and more preferably chromosome 1, q23-25, and most preferably chromosome 1, q24).

Localization studies using a Stanford G3 radiation hybrid panel mapped the TIGR gene with the D1S2536 marker nucleic acid molecules at the D1S2536 locus with a LOD score of 6.0. Other marker nucleic acid molecules in this region include: D1S210; D1S1552; D1S2536; D1S2790; SHGC-12820; and D1S2558. Other polynucleotide markers that map to such locations are known and can be employed to identify such polymorphism(s).

The genomes of animals and plants naturally undergo spontaneous mutation in the course of their continuing evolution (Gusella, J.F., *Ann. Rev. Biochem.* 55:831-854 (1986)). A "polymorphism" in the TIGR gene or its flanking regions is a variation or difference in the sequence of the TIGR gene or its flanking regions that arises in some of the members of a species. The variant sequence and the "original" sequence co-exist in the species' population. In some instances, such co-existence is in stable or quasi-stable equilibrium.

A polymorphism is thus said to be "allelic," in that, due to the existence of the polymorphism, some members of a species may have the original sequence (i.e. the original "allele") whereas other members may have the variant sequence (i.e. the variant "allele"). In the simplest case, only one variant sequence may exist, and the polymorphism is thus said to be di-allelic. In other cases, the species' population may contain multiple alleles, and the polymorphism is termed tri-allelic, etc. A single gene may have multiple different unrelated polymorphisms. For example, it

may have a di-allelic polymorphism at one site, and a multi-allelic polymorphism at another site.

The variation that defines the polymorphism may range from a single nucleotide variation to the insertion or deletion of extended regions within a gene.

- 5 In some cases, the DNA sequence variations are in regions of the genome that are characterized by short tandem repeats (STRs) that include tandem di- or tri-nucleotide repeated motifs of nucleotides. Polymorphisms characterized by such tandem repeats are referred to as "variable number tandem repeat" ("VNTR") polymorphisms. VNTRs have been used in identity and paternity analysis (Weber,
10 J.L., U.S. Patent 5,075,217; Armour, J.A.L. et al., *FEBS Lett.* 307:113-115 (1992); Jones, L. et al., *Eur. J. Haematol.* 39:144-147 (1987); Horn, G.T. et al., PCT Application WO91/14003; Jeffreys, A.J., European Patent Application 370,719; Jeffreys, A.J., U.S. Patent 5,175,082); Jeffreys, A.J. et al., *Amer. J. Hum. Genet.* 39:11-24 (1986); Jeffreys, A.J. et al., *Nature* 316:76-79 (1985); Gray, I.C. et al., *Proc. R. Acad. Soc. Lond.* 243:241-
15 253 (1991); Moore, S.S. et al., *Genomics* 10:654-660 (1991); Jeffreys, A.J. et al., *Anim. Genet.* 18:1-15 (1987); Hillel, J. et al., *Anim. Genet.* 20:145-155 (1989); Hillel, J. et al., *Genet.* 124:783-789 (1990)).

- In an alternative embodiment, such polymorphisms can be detected through the use of a marker nucleic acid molecule that is physically linked to such polymorphism(s). For this purpose, marker nucleic acid molecules comprising a nucleotide sequence of a polynucleotide located within 1 mb of the polymorphism(s), and more preferably within 100 kb of the polymorphism(s), and most preferably within 10 kb of the polymorphism(s) can be employed. Examples of such marker nucleic acids are set out in SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25.

- 30 In another embodiment a marker nucleic acid will be used that is capable of specifically detecting *TIGRmt1*, *TIGRmt2*, *TIGRmt3*, *TIGRmt4*, *TIGRmt5*, *TIGRsv1*, or a combination of these mutations. Methods to detect base(s) substitutions, base(s) deletions and base(s) additions are known in the art (i.e. methods to genotype an individual). For example, "Genetic Bit Analysis ("GBA") method is disclosed by
35 Goelet, P. et al., WO 92/15712, herein incorporated by reference, may be used for

detecting the single nucleotide polymorphisms of the present invention. GBA is a method of polymorphic site interrogation in which the nucleotide sequence information surrounding the site of variation in a target DNA sequence is used to design an oligonucleotide primer that is complementary to the region immediately adjacent to, but not including, the variable nucleotide in the target DNA. The target DNA template is selected from the biological sample and hybridized to the interrogating primer. This primer is extended by a single labeled dideoxynucleotide using DNA polymerase in the presence of two, and preferably all four chain terminating nucleoside triphosphate precursors. Cohen, D. et al., (PCT Application 5 WO91/02087) describes a related method of genotyping.

10 Other primer-guided nucleotide incorporation procedures for assaying polymorphic sites in DNA have been described (Komher, J. S. et al., *Nucl. Acids. Res.* 17:7779-7784 (1989), herein incorporated by reference; Sokolov, B. P., *Nucl. Acids Res.* 18:3671 (1990), herein incorporated by reference; Syvänen, A.-C., et al., *Genomics* 5:684 - 692 (1990), herein incorporated by reference; Kuppuswamy, M.N. et al., *Proc. Natl. Acad. Sci. (U.S.A.)* 88:1143-1147 (1991), herein incorporated by reference; 15 Prezant, T.R. et al., *Hum. Mutat.* 1:159-164 (1992), herein incorporated by reference; Uguzzoli, L. et al., *GATA* 9:107-112 (1992), herein incorporated by reference; Nyrén, P. et al., *Anal. Biochem.* 208:171-175 (1993), herein incorporated by reference).

20 The detection of polymorphic sites in a sample of DNA may be facilitated through the use of nucleic acid amplification methods. Such methods specifically increase the concentration of polynucleotides that span the polymorphic site, or include that site and sequences located either distal or proximal to it. Such amplified molecules can be readily detected by gel electrophoresis or other means.

25 Another preferred method of achieving such amplification employs the polymerase chain reaction ("PCR") (Mullis, K. et al., *Cold Spring Harbor Symp. Quant. Biol.* 51:263-273 (1986); Erlich H. et al., European Patent Appln. 50,424; European Patent Appln. 84,796, European Patent Application 258,017, European Patent Appln. 237,362; Mullis, K., European Patent Appln. 201,184; Mullis K. et al., U.S. Patent No. 30 4,683,202; Erlich, H., U.S. Patent No. 4,582,788; and Saiki, R. et al., U.S. Patent No. 4,683,194), using primer pairs that are capable of hybridizing to the proximal sequences that define a polymorphism in its double-stranded form.

35 In lieu of PCR, alternative methods, such as the "Ligase Chain Reaction" ("LCR") may be used (Barany, F., *Proc. Natl. Acad. Sci. (U.S.A.)* 88:189-193 (1991). LCR uses two pairs of oligonucleotide probes to exponentially amplify a specific

target. The sequences of each pair of oligonucleotides is selected to permit the pair to hybridize to abutting sequences of the same strand of the target. Such hybridization forms a substrate for a template-dependent ligase. As with PCR, the resulting products thus serve as a template in subsequent cycles and an exponential amplification of the desired sequence is obtained.

LCR can be performed with oligonucleotides having the proximal and distal sequences of the same strand of a polymorphic site. In one embodiment, either oligonucleotide will be designed to include the actual polymorphic site of the polymorphism. In such an embodiment, the reaction conditions are selected such that the oligonucleotides can be ligated together only if the target molecule either contains or lacks the specific nucleotide that is complementary to the polymorphic site present on the oligonucleotide. Alternatively, the oligonucleotides may be selected such that they do not include the polymorphic site (see, Segev, D., PCT Application WO 90/01069).

The "Oligonucleotide Ligation Assay" ("OLA") may alternatively be employed (Landegren, U. *et al.*, *Science* 241:1077-1080 (1988)). The OLA protocol uses two oligonucleotides which are designed to be capable of hybridizing to abutting sequences of a single strand of a target. OLA, like LCR, is particularly suited for the detection of point mutations. Unlike LCR, however, OLA results in "linear" rather than exponential amplification of the target sequence.

Nickerson, D.A. *et al.*, have described a nucleic acid detection assay that combines attributes of PCR and OLA (Nickerson, D.A. *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 87:8923-8927 (1990)). In this method, PCR is used to achieve the exponential amplification of target DNA, which is then detected using OLA. In addition to requiring multiple, and separate, processing steps, one problem associated with such combinations is that they inherit all of the problems associated with PCR and OLA.

Schemes based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide, are also known (Wu, D.Y. *et al.*, *Genomics* 4:560 (1989)), and may be readily adapted to the purposes of the present invention.

Other known nucleic acid amplification procedures, such as allele-specific oligomers, branched DNA technology, transcription-based amplification systems, or isothermal amplification methods may also be used to amplify and analyze such polymorphisms (Malek, L.T. *et al.*, U.S. Patent 5,130,238; Davey, C. *et al.*, European

Patent Application 329,822; Schuster *et al.*, U.S. Patent 5,169,766; Miller, H.I. *et al.*, PCT appln. WO 89/06700; Kwok, D. *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 86:1173 (1989); Gingras, T.R. *et al.*, PCT application WO 88/10315; Walker, G.T. *et al.*, *Proc. Natl. Acad. Sci. (U.S.A.)* 89:392-396 (1992)). All the foregoing nucleic acid amplification methods could be used to predict or diagnose glaucoma.

The identification of a polymorphism in the TIGR gene can be determined in a variety of ways. By correlating the presence or absence of glaucoma in an individual with the presence or absence of a polymorphism in the TIGR gene or its flanking regions, it is possible to diagnose the predisposition (prognosis) of an asymptomatic patient to glaucoma, related diseases, or steroid sensitivity. If a polymorphism creates or destroys a restriction endonuclease cleavage site, or if it results in the loss or insertion of DNA (e.g., a VNTR polymorphism), it will alter the size or profile of the DNA fragments that are generated by digestion with that restriction endonuclease. As such, individuals that possess a variant sequence can be distinguished from those having the original sequence by restriction fragment analysis. Polymorphisms that can be identified in this manner are termed "restriction fragment length polymorphisms" ("RFLPs"). RFLPs have been widely used in human and animal genetic analyses (Glassberg, J., UK patent Application 2135774; Skolnick, M.H. *et al.*, *Cytogen. Cell Genet.* 32:58-67 (1982); Botstein, D. *et al.*, *Ann. J. Hum. Genet.* 32:314-331 (1980); Fischer, S.G. *et al.* (PCT Application WO90/13668); Uhlen, M., PCT Application WO90/11369)). The role of TIGR in glaucoma pathogenesis indicates that the presence of genetic alterations (e.g., DNA polymorphisms) that affect the TIGR response can be employed to predict glaucoma

A preferred method of achieving such identification employs the single-strand conformational polymorphism (SSCP) approach. The SSCP technique is a method capable of identifying most sequence variations in a single strand of DNA, typically between 150 and 250 nucleotides in length (Elles, *Methods in Molecular Medicine: Molecular Diagnosis of Genetic Diseases*, Humana Press (1996), herein incorporated by reference); Orita *et al.*, *Genomics* 5: 874-879 (1989), herein incorporated by reference). Under denaturing conditions a single strand of DNA will adopt a conformation that is uniquely dependent on its sequence conformation. This conformation usually will be different, even if only a single base is changed. Most conformations have been reported to alter the physical configuration or size sufficiently to be detectable by electrophoresis. A number of protocols have been

described for SSCP including, but not limited to Lee *et al.*, *Anal. Biochem.* 205: 289-293 (1992), herein incorporated by reference; Suzuki *et al.*, *Anal. Biochem.* 192: 82-84 (1991), herein incorporated by reference; Lo *et al.*, *Nucleic Acids Research* 20: 1005-1009 (1992), herein incorporated by reference; Sarkar *et al.*, *Genomics* 13: 441-443 (1992), herein incorporated by reference).

In accordance with this embodiment of the invention, a sample DNA is obtained from a patient's cells. In a preferred embodiment, the DNA sample is obtained from the patient's blood. However, any source of DNA may be used. The DNA is subjected to restriction endonuclease digestion. TIGR is used as a probe in accordance with the above-described RFLP methods. By comparing the RFLP pattern of the TIGR gene obtained from normal and glaucomatous patients, one can determine a patient's predisposition (prognosis) to glaucoma. The polymorphism obtained in this approach can then be cloned to identify the mutation at the coding region which alters the protein's structure or regulatory region of the gene which affects its expression level. Changes involving promoter interactions with other regulatory proteins can be identified by, for example, gel shift assays using HTM cell extracts, fluid from the anterior chamber of the eye, serum, etc. Interactions of TIGR protein in glaucomatous cell extracts, fluid from the anterior chamber of the eye, serum, etc. can be compared to control samples to thereby identify changes in those properties of TIGR that relate to the pathogenesis of glaucoma. Similarly such extracts and fluids as well as others (blood, etc.) can be used to diagnosis or predict steroid sensitivity.

Several different classes of polymorphisms may be identified through such methods. Examples of such classes include: (1) polymorphisms present in the TIGR cDNA of different individuals; (2) polymorphisms in non-translated TIGR gene sequences, including the promoter or other regulatory regions of the TIGR gene; (3) polymorphisms in genes whose products interact with TIGR regulatory sequences; (4) polymorphisms in gene sequences whose products interact with the TIGR protein, or to which the TIGR protein binds.

In an alternate sub-embodiment, the evaluation is conducted using oligonucleotide "probes" whose sequence is complementary to that of a portion of SEQ ID NO: 1, SEQ ID NO: 2 SEQ ID NO: 3, SEQ ID NO: 4, or SEQ ID NO: 5. Such molecules are then incubated with cell extracts of a patient under conditions sufficient to permit nucleic acid hybridization.

In one sub-embodiment of this aspect of the present invention, one can diagnose or predict glaucoma, related diseases and steroid sensitivity by ascertaining the TIGR response in a biopsy (or a macrophage or other blood cell sample), or other cell sample, or more preferably, in a sample of bodily fluid 5 (especially, blood, serum, plasma, tears, buccal cavity, etc.). Since the TIGR gene is induced in response to the presence of glucocorticoids, a highly preferred embodiment of this method comprises ascertaining such TIGR response prior to, during and/or subsequent to, the administration of a glucocorticoid. Thus, by way of illustration, glaucoma could be diagnosed or predicted by determining whether 10 the administration of a glucocorticoid (administered topically, intraocularly, intramuscularly, systemically, or otherwise) alters the TIGR response of a particular individual, relative to that of normal individuals. Most preferably, for this purpose, at least a "TIGR gene-inducing amount" of the glucocorticoid will be provided. As used herein, a TIGR gene-inducing amount of a glucocorticoid is an amount of 15 glucocorticoid sufficient to cause a detectable induction of TIGR expression in cells of glaucomatous or non-glaucomatous individuals.

III. Methods of Administration

The agents of the present invention can be formulated according to known methods to prepare pharmacologically acceptable compositions, whereby these 20 materials, or their functional derivatives, having the desired degree of purity are combined in admixture with a physiologically acceptable carrier, excipient, or stabilizer. Such materials are non-toxic to recipients at the dosages and concentrations employed. The active component of such compositions may be 25 agents analogs or mimetics of such molecules. Where nucleic acid molecules are employed, such molecules may be sense, antisense or triplex oligonucleotides of the TIGR promoter, TIGR cDNA, TIGR intron, TIGR exon or TIGR gene.

A composition is said to be "pharmacologically acceptable" if its administration can be tolerated by a recipient patient. An agent is physiologically significant if its presence results in a detectable change in the physiology of a 30 recipient patient.

Suitable vehicles and their formulation, inclusive of other human proteins, e.g., human serum albumin, are described, for example, in Remington's Pharmaceutical Sciences (16th ed., Osol, A., Ed., Mack, Easton PA (1980)).

If the composition is to be water soluble, it may be formulated in a buffer such as phosphate or other organic acid salt preferably at a pH of about 7 to 8. If the composition is only partially soluble in water, it may be prepared as a microemulsion by formulating it with a nonionic surfactant such as Tween, 5 Pluronics, or PEG, e.g., Tween 80, in an amount of, for example, 0.04-0.05% (w/v), to increase its solubility. The term "water soluble" as applied to the polysaccharides and polyethylene glycols is meant to include colloidal solutions and dispersions. In general, the solubility of the cellulose derivatives is determined by the degree of substitution of ether groups, and the stabilizing derivatives useful herein should 10 have a sufficient quantity of such ether groups per anhydroglucose unit in the cellulose chain to render the derivatives water soluble. A degree of ether substitution of at least 0.35 ether groups per anhydroglucose unit is generally sufficient. Additionally, the cellulose derivatives may be in the form of alkali metal salts, for example, the Li, Na, K or Cs salts.

15 Optionally other ingredients may be added such as antioxidants, e.g., ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinyl pyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, 20 disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrins; chelating agents such as EDTA; and sugar alcohols such as mannitol or sorbitol.

Additional pharmaceutical methods may be employed to control the duration of action. Controlled or sustained release preparations may be achieved 25 through the use of polymers to complex or absorb the TIGR molecule(s) of the composition. The controlled delivery may be exercised by selecting appropriate macromolecules (for example polyesters, polyamino acids, polyvinyl pyrrolidone, ethylenevinylacetate, methylcellulose, carboxymethylcellulose, or protamine sulfate) and the concentration of macromolecules as well as the methods of incorporation in 30 order to control release.

Sustained release formulations may also be prepared, and include the formation of microcapsular particles and implantable articles. For preparing 35 sustained-release compositions, the TIGR molecule(s) of the composition is preferably incorporated into a biodegradable matrix or microcapsule. A suitable material for this purpose is a polylactide, although other polymers of poly-(a-

hydroxycarboxylic acids), such as poly-D-(*l*)-3-hydroxybutyric acid (EP 133,988A), can be used. Other biodegradable polymers include poly(lactones), poly(orthoesters), polyamino acids, hydrogels, or poly(orthocarbonates) poly(acetals). The polymeric material may also comprise polyesters, poly(lactic acid) or ethylene vinylacetate copolymers. For examples of sustained release compositions, see U.S. Patent No. 3,773,919, EP 58,481A, U.S. Patent No. 3,887,699, EP 158,277A, Canadian Patent No. 1176565; Sidman, U. *et al.*, *Biopolymers* 22:547 (1983), and Langer, R. *et al.*, *Chem. Tech.* 12:98 (1982).

Alternatively, instead of incorporating the TIGR molecule(s) of the composition into polymeric particles, it is possible to entrap these materials in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatine-microcapsules and poly(methylmethacrylate) microcapsules, respectively, or in colloidal drug delivery systems, for example, liposomes, albumin microspheres, microemulsions, nanoparticles, and nanocapsules or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences (1980).

In an alternative embodiment, liposome formulations and methods that permit intracellular uptake of the molecule will be employed. Suitable methods are known in the art, see, for example, Chicz, R.M. *et al.* (PCT Application WO 94/04557), Jaysena, S.D. *et al.* (PCT Application WO93/12234), Yarosh, D.B. (U.S. Patent No. 5,190,762), Callahan, M.V. *et al.* (U.S. Patent No. 5,270,052) and Gonzalezro, R.J. (PCT Application 91/05771), all herein incorporated by reference.

Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention, unless specified.

EXAMPLE 1 Single Strand Conformational Polymorphism

Single strand conformational polymorphism (SSCP) screening is carried out according to the procedure of Hue *et al.*, *The Journal of Investigative Ophthalmology* 105.4: 529-632 (1995), herein incorporated by reference. SSCP primers are constructed corresponding to sequences found within the TIGR promoter and two of exons of TIGR. The following primers are constructed: forward primer "Sk-1a": 5'-TGA GGC TTC CTC TGG AAA C-3' (SEQ ID NO: 6); reverse primer "ca2": 5'-TGA AAT CAG CAC ACC AGT AG-3' (SEQ ID NO: 7); forward primer "CA2": 5'-

GCA CCC ATA CCC CAA TAA TAG-3' (SEQ ID NO: 8); reverse primer "Pr+1": 5'-AGA GTT CCC CAG ATT TCA CC-3' (SEQ ID NO: 9); forward primer "Pr-1": 5'-ATC TGG GGA ACT CTT CTC AG-3' (SEQ ID NO: 10); reverse primer "Pr+2(4A2)": 5'-TAC AGT TGT TGC AGA TAC G-3' (SEQ ID NO: 11); forward primer "Pr-2(4A)": 5'-ACA ACG TAT CTG CAA CAA CTG-3' (SEQ ID NO: 12); reverse primer "Pr+3(4A)": 5'-TCA GGC TTA ACT GCA GAA CC-3' (SEQ ID NO: 13); forward primer "Pr-3(4A)": 5'-TTG GTT CTG CAG TTA AGC C-3' (SEQ ID NO: 14); reverse primer "Pr+2(4A1)": 5'-AGC AGC ACA AGG GCA ATC C-3' (SEQ ID NO: 15); reverse primer "Pr+1(4A)": 5'-ACA GGG CTA TAT TGT GGG-3' (SEQ ID NO: 16); forward primer "KS1X": 5'-CCT GAG ATG CCA GCT GTC C-3' (SEQ ID NO: 17); reverse primer "SK1XX": 5'-CTG AAG CAT TAG AAG CCA AC-3' (SEQ ID NO: 18); forward primer "KS2a1": 5'-ACC TTG GAC CAG GCT GCC AG-3' (SEQ ID NO: 19); reverse primer "SK3": 5'-AGG TTT GTT CGA GTT CCA G-3' (SEQ ID NO: 20); forward primer "KS4": 5'-ACA ATT ACT GGC AAG TAT GG-3' (SEQ ID NO: 21); reverse primer "SK6A": 5'-CCT TCT CAG CCT TGC TAC C-3' (SEQ ID NO: 22); forward primer "KS5": 5'-ACA CCT CAG CAG ATG CTA CC-3' (SEQ ID NO: 23); reverse primer "SK8": 5'-ATG GAT GAC TGA CAT GGC C-3' (SEQ ID NO: 24); forward primer "KS6": 5'-AAG GAT GAA CAT GGT CAC C-3' (SEQ ID NO: 25).

The locations of primers: Sk-1a, ca2, CA2, Pr+1, Pr-1, Pr+2(4A2), Pr-2(4A), Pr+3(4A), Pr-3 (4A), Pr-3(4A), Pr+2(4A1), and Pr+1(4A) are diagrammatically set forth in Figure 4. The location of primers: KS1X, SK1XX, Ks2a1, SK3, KS4, SK6A, KS5, SK8, and KS6 are diagrammatically set forth in Figure 5.

Families with a history of POAG in Klamath Falls, Oregon, are screened by SSCP according to the method of Hue *et al.*, *The Journal of Investigative Ophthalmology* 25 105.4: 529-632 (1995), herein incorporated by reference). SSCP primers SK-1a, ca2, CA2, Pr+1, Pr-2(4A), Pr+3(4A), SK1XX, and KS6 detect single strand conformational polymorphisms in this population. An SSCP is detected using SSCP primers Pr+3(4A) and Pr-2(4A). 70 family members of the Klamath Fall, Oregon are screened with these primers and the results are set forth in Table 1.

TABLE 1

	Total	SSCP+	SSCP-
Glaucoma positive individuals ¹	12	12	0
Glaucoma negative individuals	13	0	13
Spouses (glaucoma negative)	16	2	14
Others ²	29	6	23

1 = glaucoma positive individuals as determined by IOP of greater than 25 mmHg

2 = unidentified glaucoma due to the age of the individual.

A second SSCP is detected using SSCP primers Pr+1 and CA2. 14 family members of the Klamath Fall, Oregon are screened with these primers. A characteristic polymorphism is found in the 6 affected family members but absent in the 8 unaffected members. A third SSCP is detected using SSCP primers ca2 and sk-1a. The same 14 family members of the Klamath Fall, Oregon that are screened with Pr+1 and CA2 are screened with ca2 and sk-1a primers. A characteristic polymorphism is found in the 6 affected family members but absent in the 8 unaffected members. A fourth SSCP is detected using SSCP primers KS6 and SK1XX. 22 family members of the Klamath Fall, Oregon and 10 members of a Portland, Oregon pedigree are screened with these primers. A polymorphism is found in exon 3. The results are as set forth in Table 2.

TABLE 2

	Total	SSCP+	SSCP-
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Klamath Fall, Oregon

Glaucoma positive individuals ¹	3	3	0
Glaucoma negative individuals	6	0	6
Others ²	13	6	7

Portland, Oregon

Glaucoma positive individuals ¹	6	6	0
Glaucoma negative individuals	4	0	4
Others ²	0	0	0

1 = glaucoma positive individuals as determined by IOP of greater than 25 mmHg

2 = unidentified glaucoma due to the age of the individual.

EXAMPLE 2
TIGR Homologies

A novel myosin-like acidic protein termed myocilin is expressed predominantly in the photoreceptor cells of retina and is localized particularly in the 5 rootlet and basal body of connecting cilium (Kubota *et al.*, Genomics 41: 360-369 (1997), herein incorporated by reference). The myocilin gene is mapped to human chromosome 1q23-q24. The coding region of myocilin is 100 percent homologous with TIGR.

Homology searches are performed by GCG (Genetics Computer Group, 10 Madison, WI) and include the GenBank, EMBL, Swiss-Prot databases and EST analysis. Using the Blast search, the best fits are found with a stretch of 177 amino acids in the carboxy terminals for an extracellular mucus protein of the olfactory, olfactomedin and three olfactomedin-like species. The alignment presented in 15 Figure 6 shows the TIGR homology (SEQ ID NO. 27) to an expressed sequence tag (EST) sequence from human brain (ym08h12.r1)(SEQ ID NO. 28)(The WashU-Merck EST Project, 1995); the Z domain of olfactomedin-related glycoprotein from rat brain (1B426bAMZ)(SEQ ID NO. 29)(Danielson *et al.*, *Journal of Neuroscience Research* 38: 468-478 (1994), herein incorporated by reference) and the olfactomedin from olfactory tissue of bullfrogs (ranofm) (SEQ ID NO. 30)(Yokoe and Anholt, *Proc. Natl. 20 Acad. Sci.* 90: 4655-4659 (1993), herein incorporated by reference; Snyder and Anholt, *Biochemistry* 30: 9143-9153 (1991), herein incorporated by reference). These domains share very similar amino acid positions as depicted in the consensus homology of Figure 6 (SEQ ID NO. 31), with the exception being the truncated human clone in which the position with respect to its full length sequence has not been established. 25 No significant homology is found for the amino termini of these molecules.

While the invention has been described in connection with specific 30 embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features herein before set forth and as follows in the scope of the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: The Regents of the University of California
- (ii) TITLE OF INVENTION: METHODS FOR THE DIAGNOSIS,
PROGNOSIS AND TREATMENT OF GLAUCOMA AND RELATED
DISORDERS
- (iii) NUMBER OF SEQUENCES: 32
- (iv) CORRESPONDENCE ADDRESS:
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- (v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: Windows 95
(D) SOFTWARE: FastSEQ for Windows Version 2.0b
- (vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
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- (viii) ATTORNEY/AGENT INFORMATION:
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(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5300 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

ATCTTTGTTTC	AGTTTACCTC	AGGGCTATTAA	TGAAATGAAA	TGAGATAACC	AATGTGAAAG	60
TCCTATAAAC	TGTATAGCCT	CCATTCCGGAT	GTATGTCTTT	GGCAGGGATGA	AAAGAATCA	120
GGAAGAAGGA	GTATCCACGT	TAGCCAAGTG	TCCAGGCTGT	GTCTGCTCTT	ATTTTACTGA	180
CAGATGTTGC	TCCTGACAGA	AGCTATTCTT	CAGGAAACAT	CACATCCAAT	ATGGTAAATC	240
CATCAACAG	GAGCTAAGAA	ACAGGAATGA	GATGGGCACT	TGCCCAAGGA	AAAATGCCAG	300
GAGAGCAAAT	AATGATGAAA	AATAAACTTT	TCCCTTGTT	TTTAATTTC	GGAAAAAAATG	360
ATGAGGACCA	AAATCAATGA	ATAAGGAAAA	CAGCTCAGAA	AAAAGATGTT	TCCAAATTGG	420
TAATTAAGTA	TTTGTTCCTT	GGGAAGAGAC	CTCCATGTGA	GCTTGATGGG	AAAATGGAA	480
AAACGTCAAA	AGCATGATCT	GATCAGATCC	CAAAGTGGAT	TATTATTTA	AAAACCAGAT	540
GGCATCACTC	TGGGGAGGCA	AGTCAGGAA	GGTCATGTTA	GCAAAGGACA	TAACAATAAC	600
AGCAAAATCA	AAATTCCGCA	AATGCGAGGAG	AAAAATGGG	ACTGGGAAAG	CTTTCATAAC	660
AGTGATTAGG	CAGTTGACCA	TGTTCGCAAC	ACCTCCCCGT	CTATACCAGG	GAACACAAAA	720
ATTGACTGGG	CTAAGCCTGG	ACTTTCAAGG	GAAATATGAA	AAACTGAGAG	AAAACACAAA	780
GACATGGTTA	AAAGGCACC	AGAACATTGT	GAGCCTCAA	AGCAGCAGTG	CCCCTCAGCA	840
GGGACCCCTGA	GGCATTGCC	TTAGGAAGG	CCAGTTTCT	TAAGGAATCT	TAAGAAACTC	900
TTGAAAGATC	ATGAATTAA	ACCATTAA	GTATAAAACA	AATATGCGAT	GCATAATCAG	960
TTTAGACATG	GGTCCCAATT	TTATAAAGTC	AGGCATACAA	GGATAACGTG	TCCAGCTCC	1020
GGATAGGTCA	GAAATCATTA	GAAATCACTG	TGTCCCCATC	CTAACCTTTT	CAGAATGATC	1080
TGTCATAGCC	CTCACACACA	GGCCCGATGT	GTCTGACCTA	CAACCACATC	TACAACCCAA	1140
GTGCCCTAAC	CATTGTTAAC	GTGTACATCTC	AGTAGGTCCC	ATTACAAATG	CCACCTCCCC	1200
TGTGCAGCCC	ATCCCCTGCC	ACAGGAAGTC	TCCCCACTCT	AGACTTCTGC	ATCACGATGT	1260
TACAGCCAGA	AGCTCCGTGA	GGGTGAGGGT	CTGTGCTTTA	CACCTACCTG	TATGCTCTAC	1320
ACCTGAGCTC	ACTGCAACCT	CTGCCTCCCCA	GGTTCAAGCA	ATTCTCCTGT	CTCAGCCTCC	1380
CGCGTAGCTG	GGACTACAGG	CGCACGCCCG	GCTAATT	GTATTGTTAG	TAGAGATGGG	1440
GTTTCACCAT	ATTAGCCCGG	CTGGTCCTGA	ACTCCGTGACC	TCAGGTGATC	CACCCACCTC	1500
AGCCTCCTAA	AGTCCTGGGA	TTACAGGCAT	GAGTCACCGC	GGCCGGCCAA	GGGTCACTGT	1560
TTAATAAGGA	ATAACTGAA	TGTTTACTA	AACCAACAGG	GAAACAGACA	AAAGCTGTGA	1620
TAATTTCAGG	GATTCTGGG	ATGGGGAAATG	GTGCCATGAG	CTGCCCTGCC	AGTCCCAGAC	1680
CACTGGCTCT	CATCACTTTC	TTCCCTCATC	CTCATTTC	GGCTAAGTTA	CCATTTTATT	1740
CACCATGCTT	TTGTGGTAAG	CCTCCACATC	GTTACTGAAA	TAAGAGTATA	CATAAAACTAG	1800
TTCCATTGTTG	GGCCATCTGT	GTGTGTGTAT	AGGGGAGGAG	GGCATAACCC	AGAGACTCCT	1860
TGAAGCCCCC	GGCAGAGGTT	TCCCTCTCCAG	CTGGGGGAGC	CCTGCAAGCA	CCCCGGGTCC	1920
TGGGTGTCT	GAGCAACCTG	CCAGCCCGTG	CCACTGGTTG	TTTTGTTATC	ACTCTCTAGG	1980
GACCTGTTGC	TTTCTATTT	TGTGTGACTC	GTTCATTATC	CCAGGCATTC	ATTGACAATT	2040
TATTGAGTAC	TTATATCTGC	CAGACACCAG	AGACAAAATG	GTGAGCAAAG	CAGTCACATGC	2100
CCTACCTTCG	TGGAGGTGAC	AGTTCTCAT	GGAAGACGTG	CAGAAGAAAA	TTAATAGCCA	2160
GCCAACCTAA	ACCCAGTGCT	GAAAGAAAGG	AAATAAACAC	CATCTTGAAAG	AATTGTGCGC	2220
AGCATCCCTT	AAACAAGGCCA	CCTCCCTAGC	GCCCCCTGCT	GCCTCCATCG	TGCCCGGAGG	2280
CCCCCAAGCC	CGAGTCTTCC	AAGCCTCCTC	CTCCATCAGT	CACAGCCTG	CAGCTGGCCT	2340
GCCTCGCTTC	CCGTGAATCG	TCTGGTGC	TCTGAGCTGG	AGACTCCTTG	GCTCCAGGCT	2400
CCAGAAAGGA	AATGGAGAGG	GAAAAGTAGTC	TAACGGAGAA	TCTGGAGGGG	ACAGTGTGTT	2460
CTCAGAGGGA	AAGGGCCTC	CACGTCCAGG	AGAATTCCAG	GAGGTGGGGA	CTGCAGGGAG	2520
TGGGGACGCT	GGGGCTGAGC	GGGTGCTGAA	AGGCAGGAAG	GTGAAAAGGG	CAAGGCTGAA	2580
GCTGCCAGA	TGTTCACTGT	TGTTCACTGGG	GCTGGGAGTT	TTCCGTTGCT	TCCTGTGAGC	2640
CTTTTTATCT	TTTCTCTGCT	TGGAGGAGAA	GAAGTCTATT	TCATGAAGGG	ATGCAGTTTC	2700
ATAAAAGTCAG	CTGTTAAAT	TCCAGGGTGT	GCATGGGTTT	TCCTTCACGA	AGGCCTTTAT	2760
TTAATGGGAA	TATAGGAAGC	GAGCTCATT	CCTAGGCCGT	TAATTACCGG	AAGAAGTGAC	2820
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TGCAAGACGG	TCGAAAACCT	TGGAATCAGG	AGACTCGGTT	TTCTTCTGG	TTCTGCCATT	2940
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ATAAAAGACCC	TTGCAGCTCT	CGTGTCTGT	GAACACTTCC	CTGTGATTT	CTGTGAGGGG	3060
GGATGTTGAG	AGGGGAAGGA	GGCAGAGCTG	GAGCAGCTGA	GCCACAGGGG	AGGTGGAGGG	3120
GGACAGGAAG	GCAGGCAGAA	GCTGGGTGCT	CCATCAGTCC	TCACTGATCA	CGTCAGACTC	3180
CAGGACCGAG	AGCCACAATG	CTTCAGGAA	GCTCAATGAA	CCCAACAGCC	ACATTTTCC	3240
TCCCTAAGCA	TAGACAATGG	CATTGCCAA	TAACCAAAAA	GAATGCAGAG	ACTAACTGGT	3300
GGTAGTTTT	GCCTGGCATT	CAAAAATGG	GCCAGAGCAA	GTGAAAATG	CCAGAGATTG	3360

TTAAACCTTT	CACCC TGACC	AGC ACCCCC AC	GCAG CTC AGC	AGT GACT GCT	GAC AGC ACGG	3420
AGTGACCTGC	AGCG CAGGGG	AGG AGA AGAA	AAAG AGAGGG	ATAG TGT ATG	AGCA AGA AAG	3480
ACAGATTCA	TCAAGGGCAG	TGGA ATTGA	CCACAGGGAT	TATAGTCCAC	GTGAT CCTGG	3540
GTTCTAGGAG	GCAGGGCTAT	ATT GTGGGGG	AAAAAATCA	GTTCAAGGGA	AGTCGGAGA	3600
CCTGATTCT	AATACTATAT	TTT CCTTTA	CAAG CTGAGT	AATT CTGAGC	AAGT CACAAG	3660
GTAGTAATG	AGG CTGTAAG	ATTACTTAGT	TTCT CCTTAT	TAGGA ACTCT	TTT TCTCTGT	3720
GGAGTTAGCA	GCACAAAGGGC	AAT CCC GTTT	CTTTA ACAG	GAAG AAAACA	TTCCAAGAG	3780
TAAAGCCAAA	CAG ATT CAAG	CCTAG GTCTT	GCTG ACTATA	TGATT GGTTT	TTT GAAAAT	3840
CATTTCAGCG	ATGTTTACTA	TCTGATTCA	AAAATGAGAC	TAGT ACCCTT	TGGT CAGCTG	3900
TAAACAAACA	CCC ATT TGTA	AAT GTCTCA	GTTCAGGCTT	AACT GCAGAA	CCAATCAAAT	3960
AAGAATAGAA	TCTT TAGAGC	AAACT GTGTT	TCTCC ACTCT	GGAGGTGAGT	CTGCCAGGGC	4020
AGTTTGAAA	TATTT ACTTC	ACAAGT ATTG	ACACT GTTGT	TGGT ATTAAAC	AACATAAAGT	4080
TGCTCAAAGG	CAAT CATTAT	TTCAAG GTGC	TTAAAG TTAC	TTCTGACAGT	TTT GGTTATAT	4140
TTAT TGGCTA	TTGCC ATT TTG	CTTTT GTTT	TTT CTCTTTG	GGTTT ATTAA	TGTAAAGCAG	4200
GGATTATTAA	CCTACAGTCC	AGAAAGCCTG	TGA ATT TGAA	TGAGGAAAAA	ATTAC ATTTT	4260
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CTCAAAGTGG	TAATAACAGT	ACCT GTGATT	TTGTC ATTAC	CAATAGAAAT	CACAGACATT	4380
TTATACTATA	TTACAGTTGT	TGCAGA TAGC	TTGTAAGTGA	AAT ATT TATA	CTCAAAACTA	4440
CTTTGAAATT	AGACCTCCTG	CTGCA TCTTG	TTTTA ACAT	ATTAA TAAA	CAT GTTT AAA	4500
ATTTTGATAT	TTTGATAATC	ATATTTCATT	ATCATT GTT	TCCTT GTAA	TCTAT ATTTT	4560
ATATATTG	AAACAT CTT	CTGAGAAGAG	TTCCCAGAT	TTCACCAATG	AGGTCTTGG	4620
CATG CACACA	CACAGAGTAA	GAAC TGATT	AGAGGCTAAC	ATTGACATTG	GTGCC TGAGA	4680
TGCAAGACTG	AAATTAGAAA	GTTC TCCC AA	AGATA CACAG	TTGTTT TAAA	GCTAGGGGTG	4740
AGGGGGAAA	TCTCCC GTT	CTATAGGAAT	GCTCT CCGT	GAGC CTGGTA	GGGTGCTGTC	4800
CTTGTGTTCT	GGCTGGCTGT	TATTTT CTC	TGTCC CTGCT	ACGTCTTAAA	GGACTT GTTT	4860
GGATCTCCAG	TTCT TAGCAT	AGTGC CTGGC	ACAGTGCAGG	TTCTCAATGA	TTT GCAGAG	4920
TGAATGGAAA	TATAAACTAG	AAATATATCC	TTGTTGAAAT	CAGCACACCA	GTAGT CCTGG	4980
TGTAAGTGTG	TGTAC GTGTG	TGTGT GTGTG	TGTGT GTGTG	TGTAAAACCA	GGTGGAGATA	5040
TAGGAACTAT	TATTGGGGTA	TGGGTG CATA	AATTGGGATG	TTCTTTT TAA	AAAGAAACTC	5100
CAAACAGACT	TCTGG AAGGT	TATTTT CTA	GAATCTGCT	GGCAGCGTGA	AGGCAACCCC	5160
CCTGTGCACA	CCCCCACCA	GCCTCAC GTG	GCCACCTCTG	TCTT CCCCCA	TGAAGGGCTG	5220
GCTCCCCAGT	ATATATAAAC	CTCTCTGGAG	CTCGGGCATG	AGCCAGCAAG	GCCACCCATC	5280
CAGGCACCTC	TCAGCACAGC					5300

(2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 5304 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

ATCTTTGTT	AGTTTACCTC	AGGGCTATT	TGAAATGAAA	TGAGATAACC	AAT GTGAAAG	60
TCCTATAAAC	TGTATAGCCT	CCATT CGGAT	GTAT GTCTT	GGCAGGATGA	TAAAGAATCA	120
GGAAGAAGGA	GTAT CCACGT	TAGCCAAGTG	TCCAGGCTGT	GTCTGCTCTT	ATTTT AGTGA	180
CAGAT GTTG	TCCTGACAGA	AGCT ATTCTT	CAGGAAACAT	CACATCCAAT	ATCGTAAATC	240
CATCAAACAG	GAGCTAAGAA	ACAGGAATGA	GATGGGCACT	TGCCCAAGGA	AAAATGCCAG	300
GAGAGCAAAT	AATGATGAAA	AATAAACTTT	TCCC TTGTT	TTTAATTCA	GGAAAAAAATG	360
ATGAGGACCA	AAATCAATGA	ATAAGGAAAA	CAGCTCAGAA	AAAAGATGTT	TCCAAT TTG	420
TAATTAAGTA	TTT GTT CCTT	GGGAAGAGAC	CTCCAT GTGA	GCTT GATGGG	AAAATGGGAA	480
AAACGTCAA	AGC ATGATCT	GATCAGATCC	CAAAGTGGAT	TATTATTTA	AAAACCAGAT	540
GGCATCACTC	TGGGGAGGCC	AGTT CAGGAA	GGTCAT GTTA	GCAAAGGACA	TAACAATAAC	600
AGCAAAATCA	AAATTCCCGA	AATG CAGGAG	GAAAATGGGG	ACTGGGAAAG	CTTT CATAAC	660
AGTGATTAGG	CAGTTGACCA	TGTT CGCAAC	ACCT CCCC GT	CTAT ACCAGG	GAACACAAAA	720
ATTGACTGGG	CTAAGCCTGG	ACTTTCAAGG	GAAATATGAA	AAACTGAGAG	CAAACAAAAA	780
GACATGGTTA	AAAGGCAACC	AGAACATTGT	GAGC CTTCAA	AGCAGCAGTG	CCCCTCAGCA	840
GGGACCCCTGA	GGCATT TGCC	TTT TAGGAAGG	CCAGTTTCT	TAAGGAATCT	TAAGAAACTC	900

TTGAAAGATC	ATGAATTATA	ACCATTTAA	GTATAAAACA	AATATGCAT	GCATAATCAG	960
TTTAGACATG	GGTCCCAATT	TTATAAAGTC	AGGCATACAA	GGATAACGTG	TCCCAGCTCC	1020
GGATAGGTCA	GAAATCATTA	GAAATCACTG	TGTCCCCATC	CTAACTTTT	CAGAATGATC	1080
TGTCATAGCC	CTCACACACA	GGCCCGATGT	GTCTGACCTA	CAACCACATC	TACAACCCAA	1140
GTGCCTAAC	CATTGTTAAC	GTGTCATCTC	AGTAGGTCCC	ATTACAAATG	CCACCTCCCC	1200
TGTGAGGCC	ATCCCCTC	ACAGGAAGTC	TCCCCACTCT	AGACTTCCTG	ATCACGATGT	1260
TACAGCCAGA	AGCTCCGTGA	GGGTGAGGGT	CTGTGCTTAA	CACCTACCTG	TATGCTCTAC	1320
ACCTGAGCTC	ACTGCAACCT	CTGCCTCCC	GGTTCAAGCA	ATTCTCCCTG	CTCAGCCTCC	1380
CGCGTAGCTG	GGACTACAGG	CGCACGCCCG	GCTAATTTTT	GTATTGTTAG	TAGAGATGGG	1440
GTTCACCAC	ATTAGCCCCG	CTGGTCCTG	ACTCCGACC	TCAGGTGATC	CACCCACCTC	1500
AGCCTCTAA	AGTGCTGGG	TTACAGGCAT	GAGTCACCGC	GGCGGCCAA	GGTCAGTGT	1560
TTAATAAGGA	ATAACTGAA	TGTTTACTA	AACCAACAGG	GAAACAGACA	AAAGCTGTGA	1620
TAATTCTAGG	GATTCTGGG	ATGGGAAATG	GTGCCATGAG	CTGCTGCT	AGTCCCAGAC	1680
CACTGGTCT	CATCACTTC	TTCCCTCATC	CTCATTTC	GGCTAAGTTA	CCATTTATT	1740
CACCATGCTT	TTGTGGTAAG	CCTCCACATC	GTTACTGAA	TAAGAGTTA	CATAAACTAG	1800
TTCCATTG	GGCCATCTGT	GTGTTGTTAT	AGGGGAGGAG	GGCATACCCC	AGAGACTCCT	1860
TGAAGCCCC	GGCAGAGGTT	TCCCTCCAG	CTGGGGGAGC	CCTGCAAGCA	CCCCGGGTCC	1920
TGGGTGTCT	GAGCAACCTG	CCAGCCCGTG	CCACTGGTTG	TTTGTATC	ACTCTCTAGG	1980
GACCTGTTG	TTTCTATTT	TGTTGACTC	GTTCATTATC	CCAGGCATTC	ATTGACAATT	2040
TATTGAGTAC	TTATATCTGC	CAGACACCAG	AGACAAAATG	GTGAGCAAAG	CAGTCACTGC	2100
CCTACCTTCG	TGGAGGTGAC	AGTTTCTCAT	GGAAGACGTG	CAGAAGAAAA	TTAATAGCCA	2160
GCCAACCTAA	ACCCAGTGCT	GAAAGAAAGG	AAATAAACAC	CATCTTGAG	AATTGTCGCG	2220
AGCATCCCTT	AAACAGGCCA	CCTCCCTAGC	GCCCCCTGCT	GCCTCCATCG	TGCCCCGGAGG	2280
CCCCCAAGCC	CGAGCTTCC	AAGCCTCCTC	CTCCATCATG	CACAGCGCTG	CAGCTGGCCT	2340
GCCTCGCTTC	CCGTGAATCG	TCTCTGGTCA	TCTGAGCTGG	AGACTCCTTG	GCTCCAGGCT	2400
CCAGAAAGGA	AATGGAGAGG	GAAACTAGTC	TAACGGAGAA	TCTGGAGGGG	ACAGTGTITC	2460
CTCAGAGGGA	AAGGGGCTC	CACGTCCAGG	AGAATTCCAG	GAGGTGGGGA	CTGCAGGGAG	2520
TGGGGACGCT	GGGGCTGAGC	GGGTGCTGAA	AGGCAGGAAG	GTGAAAAGGG	CAAGGCTGAA	2580
GCTGCCAGA	TGTTCACTGT	TGTTCACGGG	GCTGGGAGTT	TTCCGTTGCT	TCCTGTGAGC	2640
CTTTTATCT	TTTCTCTGCT	TGGAGGAGAA	GAAGTCTATT	TCATGAAGGG	ATGCAGTTTC	2700
ATAAAAGTCAG	CTGTTAAAAT	TCCAGGGTGT	GCATGGGTTT	TCCTTCACGA	AGGCCTTTAT	2760
TTAATGGGAA	TATAGGAAGC	GAGCTATT	CCTAGGCCGT	TAATTCACTG	AAGAAGTGAC	2820
TGGAGTCTTT	TCTTCATGT	CTTCTGGGCA	ACTACTCAGC	CCTGTGGTGG	ACTTGGCTTA	2880
TGCAAGACGG	TCGAAAACCT	TGGAATCAGG	AGACTCGGTT	TTCTTCTGG	TTCTGCCATT	2940
GGTTGGCTGT	GCGACCGTGG	GCAAGTGTCT	CTCCTCCCT	GGGCCATAGT	CTTCTCTGCT	3000
ATAAAAGACCC	TTGCAGCTCT	CGTGTCTGT	GAACACTTCC	CTGTGATTCT	CTGTGAGGGG	3060
GGATGTTGAG	AGGGGAAGGA	GGCAGAGCTG	GAGCAGCTG	CCCACAGGGG	AGTGGAGGGG	3120
GGACAGGAAG	GCAGGCAGAA	GCTGGGTGCT	CCATCAGTCC	TCACTGATCA	CGTCAGACTC	3180
CAGGACCGAG	AGCCACAATG	CTTCAGGAAA	GCTCAATGAA	CCCAACAGCC	ACATTTCCCT	3240
TCCCTAACGA	TAGACAATGG	CATTGCCAA	TAACCAAAA	GAATGCAGAG	ACTAACTGGT	3300
GGTAGCTTT	GCCTGGCATT	AAAAACTGG	GCCAGAGCAA	GTGGAAAATG	CCAGAGATTG	3360
TTAAACTTTT	CACCCCTGACC	AGCACCCCCAC	GCAGCTCAGC	AGTGAATGCT	GACAGCACGG	3420
AGTGACCTGC	AGCGCAGGGG	AGGAGAAGAA	AAAGAGAGGG	ATAGTGTATG	AGCAAGAAAG	3480
ACAGATTCTAT	TCAAGGGCAG	TGGAATTG	CCACAGGGAT	TATAGTCCAC	GTGATCCTGG	3540
GTTCTAGGAG	GCAGGGCTAT	ATTGTGGGG	AAAAAAATCA	GTTCAAGGGG	AGTCGGGAGA	3600
CCTGATTTCT	AATACTATAT	TTTCTCTTAA	CAAGCTGAGT	AATTCTGAGC	AAGTCACAAG	3660
GTAGTAAC	AGGCTGTAAG	ATTACTTAGT	TTCTCCTTAT	TAGGAACCTCT	TTTCTCTGCT	3720
GGAGTTAGCA	GCACAAGGGC	AATCCCCTT	CTTTTAACAG	GAAGAAAACA	TTCTTAAGAG	3780
TAAAGCCAAA	CAGATTCAAG	CCTAGGTCTT	GCTGACTATA	TGATTGGTTT	TTTAAAAAAAT	3840
CATTTCAGCG	ATGTTTACTA	TCTGATTCA	AAAATGAGAC	TAGTACCCCT	TGGTCAGCTG	3900
TAAACAAACA	CCCATTGTA	AATGTCCTAA	GTTCAGGCTT	AACTGCAGAA	CCAATCAAAT	3960
AAGAATAGAA	TCTTGTAGGC	AAACTGTGTT	TCTCCACTCT	GGAGGTGAGT	CTGCCAGGGC	4020
AGTTTGGAAA	TATTTACTTC	ACAAGTATTG	ACACTGTTGT	TGGTATTAAC	ACATAAAAGT	4080
TGCTCAAAGG	CAATCATTAT	TTCAAGTGGC	TTAAAGTTAC	TTCTGACAGT	TTTGGTATAT	4140
TTATTGGCTA	TTGCCATTG	CTTTTGT	TTTCTCTT	GGTTTATTAA	TGTAAGCAG	4200
GGATTATTAA	CCTACAGTCC	AGAAAGCCTG	TGAATTGAA	TGAGGAAAAA	ATTACGTTTT	4260
TATTTTAC	ACCTTCTAAC	TAAATTAAAC	ATTTTATTCC	ATTGCGAATA	GAGCCATAAA	4320
CTCAAAGTGG	TAATAAGAGT	ACCTGTGATT	TTGTCATTAC	CAATAGAAAT	CACAGACATT	4380
TTATACATATA	TTACAGTTGT	TGCAAGGTACG	TTGTAAGTGA	AATATTATA	CTCAAAACTA	4440
CTTGAAATT	AGACCTCCTG	CTGGATCTTG	TTTTAACAT	ATTAATAAAA	CATGTTAAA	4500

ATTTTGATAT	TTTGATAATC	ATATTCATT	ATCATTGTT	TCCTTGTAA	TCTATATTTT	4560
ATATATTGAA	AAACATCTTT	CTGAGAAGAG	TTCCCCAGAT	TTCACCAATG	AGGTTCTTGG	4620
CATGCACACA	CACAGAGTAA	GAACGTGATT	AGAGGCTAAC	ATTGACATTG	GTGCCCTGAGA	4680
TGCAAGACTG	AAATTAGAAA	GTTCTCCCAA	AGATACACAG	TTGTTTAA	GCTAGGGGTG	4740
AGGGGGGAAA	TCTGCCGCTT	CTATAGGAAT	GCTCTCCCTG	GAGCCTGGTA	GGGTGCTGTC	4800
CTTGTGTTCT	GGCTGGCTGT	TATTTTCTC	TGTCCCTGCT	ACGTCTTAAA	GGACTTGT	4860
GGATCTCCAG	TTCCTAGCAT	AGTGCCTGGC	ACAGTGCAGG	TTCTCAATGA	GTTTGCAGAG	4920
TGAATGGAAA	TATAAACTAG	AAATATATCT	TTGTTGAAAT	CAGCACACCA	GTAGTCCTGG	4980
TGTAAGTGTG	TGTACCGTGTG	TGTGTGTGTG	TGTGTGTGTG	TGTGTGTAAA	ACCAGGTGGA	5040
GATATAGGAA	CTATTATTGG	GGTATGGGTG	CATAAATTGG	GATGTTCTTT	TTAAAAAGAA	5100
ACTCCAAAAC	GACTTCTGGA	AGGTTATTTT	CTAAGAATCT	TGCTGGCAGC	GTGAAGGCAA	5160
CCCCCCCCTGTG	CACAGCCCCA	CCCAGCCTCA	CGTGGCCACC	TCTGTCTTCC	CCCATGAAGG	5220
GCTGGCTCCC	CA GTATATAT	AAACCTCTCT	GGAGCTCGGG	CATGAGCCAG	CAAGGCCACC	5280
CATCCAGGCA	CCTCTCAGCA	CAGC				5304

(2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 6169 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATCTTTGTTCA	AGTTTACCTC	AGGGCTATTAA	TGAAATGAAA	TGAGATAACC	AATGTGAAAG	60
TCCTATAAAC	TGTATAGCCT	CCATTGCGAT	GTATGTCTTT	GGCAGGATGA	AAAAGAATCA	120
GGAAAGAAGGA	GTATCCACGT	TAGCCAAGTG	TCCAGGCTGT	GTCTGCTCTT	ATTTTAGTGA	180
CAGATGTTGC	TCCTGACAGA	AGCTATTCTT	CAGGAAACAT	CACATCCAAT	ATGGTAAATC	240
CATCAAACAG	GAGCTAAGAA	ACAGGAATGA	GATGGGCACT	TGCCCAAGGA	AAAATGCCAG	300
GAGAGCAAAT	AATGATGAAA	AATAAACTTT	TCCCTTGTGTT	TTTAATTTC	GGAAAAAAATG	360
ATGAGGACCA	AAATCAATGA	ATAAGGAAAA	CAGCTCAGAA	AAAAGATGTT	TCCAAATTGG	420
TAATTAAGTA	TTTGTCTCTT	GGGAAGAGAC	CTCCATGTGA	GCTTGATGGG	AAAATGGGAA	480
AAACGTCAAA	AGCATGATCT	GATCAGATCC	CAAAGTGGAT	TATTATTAA	AAAACCAGAT	540
GGCATCACTC	TGGGGAGGCA	AGTTCAAGGAA	GGTCATGTTA	GCAAAGGACA	TAACAATAAC	600
AGCAAAATCA	AAATTCCGCA	AATGCAGGAG	AAAAATGGGG	ACTGGGAAAG	CTTTCATAAAC	660
AGTGATTAGG	CAGTTGACCA	TGTTCGCAAC	ACCTCCCCGT	CTATACCAGG	GAACACAAAA	720
ATTGACTGGG	CTAAGCCTGG	ACTTTCAAGG	GAAATATGAA	AAACTGAGAG	CAAAACAAAA	780
GACATGGTTA	AAAGGCAACC	AGAACATTGT	GAGCCTTCAA	ACGAGCAGTG	CCCTCAGCA	840
GGGACCCCTGA	GGCATTGCC	TTTAGGAAGG	CCAGTTTCT	TAAGGAATCT	TAAGAAACTC	900
TTGAAAGATC	ATGAATTAA	ACCATTAA	GTATAAAACA	AATATGCCAT	GCATAATCAG	960
TTTAGACATG	GGTCCCAATT	TTATAAAAGTC	AGGCATACAA	GGATAACGTG	TCCCAGCTCC	1020
GGATAGGTCA	GAAATCATTAA	GAAATCACTG	TGTCCCCATC	CTAACCTTTT	CAGAATGATC	1080
TGTCATAGCC	CTCACACACA	GGCCCGATGT	GTCTGACCTA	CAACCACATC	TACAACCCAA	1140
GTGCCCTAAC	CATTGTTAAC	GTGTCACTC	AGTAGGTCCC	ATTACAAATG	CCACCTCCCC	1200
TGTGCAGCCC	ATCCCCTC	ACAGGAAGTC	TCCCCACTCT	AGACTTCTGC	ATCACGATGT	1260
TACAGCCAGA	AGCTCCGTGA	GGGTGAGGGT	CTGTGCTTTA	CACCTACCTG	TATGCTCTAC	1320
ACCTGAGCTC	ACTGCAACCT	CTGCCCTCCCA	GGTCAAGCA	ATTCTCTGT	CTCAGCCTCC	1380
CGCGTAGCTG	GGACTACAGG	CGCACGCCCG	GCTAATTTTT	GTATTGTTAG	TAGAGATGGG	1440
GTTTCACCAT	ATTAGCCCAG	CTGGTCTTGA	ACTCCTGACC	TCAGGTGATC	CACCCACCTC	1500
AGCCCTCTAA	AGTGTGGGA	TTACAGGCAT	GAGTCACCGC	GGCCGGCCAA	GGGTCACTGT	1560
TTAATAAGGA	ATAACTTGAA	TGGTTTACTA	AACCAACAGG	AAAACAGACA	AAAGCTGTGA	1620
TAATTTCAAGG	GATTCTTGGG	ATGGGGAATG	GTGCCATGAG	CTGCCCTGCCT	AGTCCCAGAC	1680
CACTGGCTCT	CATCACTTTC	TTCCCTCATC	CTCATTTCA	GGCTAAGTTA	CCATTITATT	1740
CACCATGCTT	TTGTGGTAAG	CCTCCACATC	GTTACTGAAA	TAAGAGTATA	CATAAAACTAG	1800
TTCCATTGTC	GGCCATCTGT	GTGTGTGTAT	AGGGGAGGAG	GGCATACCCC	AGAGACTCCT	1860
TGAAGCCCCC	GGCAGAGGTT	TCCTCTCCAG	CTGGGGGAGC	CCTGCAAGCA	CCCCGGGTCC	1920
TGGGTGTCT	GAGCAACCTG	CCAGCCCCGTG	CCACTGGTTG	TTTTGTTATC	ACTCTCTAGG	1980
GACCTGTTGC	TTTCTATTTC	TGTGTGACTC	GTTCAATTATC	CCAGGCATTTC	ATTGACAATT	2040

TATTGAGTAC	TTATATCTGC	CAGACACCAAG	AGACAAAATG	GTGAGCAAAG	CAGTCACTGC	2100
CCTACCTTCG	TGGAGGTGAC	AGTTTCTCAT	GGAAGACGTG	CAGAAGAAAA	TTAATAGCCA	2160
GCCAACCTAA	ACCCAGTGCT	GAAAGAAAGG	AAATAAACAC	CATCTTGAAG	AATTGTGCGC	2220
AGCATCCCTT	AACAAGGCCA	CCTCCCTAGC	GCCCCCTGCT	GCCTCCATCG	TGCCCAGGAGG	2280
CCCCCAAGCC	CGAGTCTTCC	AAGCCTCCTC	CTCCATCAGT	CACAGCGCTG	CAGCTGGCCT	2340
GCCTCGCTTC	CCGTGAATCG	TCTGGTGCA	TCTGAGCTGG	AGACTCCTTG	GCTCCAGGCT	2400
CCAGAAAGGA	AATGGAGAGG	GAAACTAGTC	TAACGGAGAA	TCTGGAGGGG	ACAGTGTTC	2460
CTCAGACGGG	AAGGGGCCTC	CACGTCCAGG	AGAATTCCAG	GAGGTGGGGA	CTGCAGGGAG	2520
TGGGACGCT	GGGGCTGAGC	GGGTGCTGAA	AGGCAGGAAG	GTGAAAAGGG	CAAGGCTGAA	2580
GCTGCCAGA	TGTTCACTGT	TGTTCACGGG	GCTGGGAGTT	TTCCGTTGCT	TCCTGTGAGC	2640
CTTTTATCT	TTTCTCTGCT	TGGAGGAGAA	GAAGCTTATT	TCATGAAGGG	ATGCAGTTTC	2700
ATAAAAGTCAG	CTGTTAAAT	TCCAGGGTGT	GCATGGGTT	TCCTTCACGA	AGGCCTTTAT	2760
TTAATGGGAA	TATAGGAAGC	GAGCTCATTT	CCTAGGCCGT	TAATTACACGG	AAGAACTGAC	2820
TGGAGTCTTT	TCTTCATGT	CTTCTGGGCA	ACTACTCAGC	CCTGTGGTGG	ACTTGGCTTA	2880
TGCAAGACGG	TCGAAAACCT	TGGAATCAGG	AGACTCGGTT	TTCTTCTGG	TTCTGCCATT	2940
GGTTGGCTGT	GCGACCGTGG	GCAAGTGTCT	CTCCTTCCCT	GGGCCATAGT	CTTCTCTGCT	3000
ATAAAGACCC	TTGCAGCTCT	CGTGTCTGT	GAACACTTCC	CTGTGATTCT	CTGTGAGGGGG	3060
GGATGTTGAG	AGGGGAAGGA	GGCAGAGCTG	GAGCAGCTGA	GCCACAGGGG	AGGTGGAGGG	3120
GGACAGGAAG	GCAGGCAGAA	GCTGGGTGCT	CCATCAGTCC	TCACTGATCA	CGTCAGACTC	3180
CAGGACCGAG	AGCCACAATG	CTTCAGGAAA	GCTCAATGAA	CCCAACAGGC	ACATTTCCCT	3240
TCCCTAACGA	TAGACAATGG	CATTGCGAA	TAACCAAAAA	GAATGCAGAG	ACTAACTGGT	3300
GGTAGCTTTT	GCCTGGCATT	CAAAAACCTGG	GCCAGAGCAA	GTGGAAAATG	CCAGAGATTG	3360
TTAAACTTTT	CACCCCTGACC	AGCACCCCCAC	GCAGCTCAGC	AGTGAATGCT	GACACCACGG	3420
AGTGACCTGC	AGCGCAGGGG	AGGAGAAGAA	AAAGAGAGGG	ATAGTGTATG	AGCAAGAAAG	3480
ACAGATTCAAT	TCAAGGGCAG	TGGGAATTGA	CCACAGGGAT	TATAGTCCAC	GTGATCCTGG	3540
GTTCTAGGAG	GCAGGGCTAT	ATTGTGGGGG	GAAAAAAATCA	GTTCAAGGGAA	AGTCAGGAGA	3600
CCTGATTTCT	AATACTATAT	TTTCTCTTTA	CAAGCTGAGT	AATTCTGAGC	AAAGTCACAAG	3660
GTAGTAAC TG	AGGCTGTAAG	ATTACTTAGT	TTCTCTTAT	TAGGAACCT	TTTCTCTGT	3720
GGAGTTAGCA	GCACAAGGGC	AATCCCGTTT	CTTTTAACAG	GAAGAAAACA	TTCTTAAGAG	3780
TAAAGCCAAA	CAGATTCAAG	CCTAGGTCTT	GCTGACTATA	TGATGGTTT	TTTGAAAAT	3840
CATTTCAGCG	ATGTTTACTA	TCTGATTCA	AAAATGAGAC	TAGTACCCCT	TGGTCAGCTG	3900
TAAACAAACA	CCCAGTTGTA	AATGTCTCAA	GTTCAAGGCTT	AACTGCAGAA	CCAATCAAAA	3960
AGAATAGAAT	CTTTAGAGCA	AACTGTGTTT	CTCCACATCT	GGAGGTGAGT	CTGCCAGGGC	4020
AGTTTGGAAA	TATTTACTTC	ACAAGTATTG	ACACTGTTGT	TGGTATTAAC	AAACATAAAAGT	4080
TGCTCAAAGG	CAATCATTAT	TTCAAGTGGC	TTAAAGTTAC	TTCTGACAGT	TTTGGTATAT	4140
TTATTGGCTA	TTGCCATTG	CTTTTTGTTT	TTTCTCTTIG	GGTTTATTAA	TGTAAAGCAG	4200
GGATTATTAA	CCTACAGTCC	AGAAAGCCTG	TGAATTGAA	TGAGGAAAAAA	ATTACATTTT	4260
TGTTTTTAC	ACCTTCTAAC	AAATTTAAC	ATTTTATTCC	ATTGCGAATA	GAGCCATAAA	4320
CTCAAAGTGG	TAATAAACAGT	ACCTGTGATT	TTGTCAATTAC	CAATAGAAAT	CACAGACATT	4380
TTATRACTATA	TTACAGTTGT	TGCAGATACG	TTGTAAGTGA	AATATTATA	CTCAAAACTA	4440
CTTTGAAATT	AGACCTCCG	CTGGATCTTG	TTTTTAACAT	ATTAATAAAA	CATGTTAAA	4500
ATTTTGATAT	TTTGATAATC	ATATTTCTT	ATCATTGTT	TCCTTTGTAA	TCTATATTTT	4560
ATATATTGAA	AAACATCTTT	CTGAGAAGAG	TTCCCCAGAT	TTCACCAATG	AGGTTCTTGG	4620
CATGACACACA	CACAGAGTAA	GAACGTGATT	AGAGGCTAAC	ATTGACATTG	GTGCCCTGAGA	4680
TGCAAGACTG	AAATTAGAAA	GTTCTCCCAA	AGATACACAG	TTGTTTAAA	GCTAGGGGTG	4740
AGGGGGGAAA	TCTGCCGCTT	CTATAGGAAT	GCTCTCCCTG	GAGCCTGGTA	GGGTGCTGTC	4800
CTTGTGTTCT	GGCTGGCTGT	TATTTTCTC	TGTCCCTGCT	ACGTCTTAAA	GGACTTGT	4860
GGATCTCCAG	TTCCTAGCAT	AGTGCCTGGC	ACAGTGCAGG	TTCTCAATGA	GTTCAGAG	4920
TGAATGGAAA	TATAAACTAG	AAATATATCC	TTGTTGAAAT	CAGCACACCA	GTAGTCCTGG	4980
TGTAAGTGTG	TGTACGTGTG	TGTGTGTGTG	TGTGTGTGTG	TGTAACACCA	GGTGGAGATA	5040
TAGGAACATAT	TATTGGGTA	TGGGTGCATA	AATTGGGATG	TTCTTTTAA	AAAGAAAATC	5100
CAAACAGACT	TCTGGAAGGT	TATTTCTAA	GAATCTGCT	GGCAGCGTGA	AGGCAACCCC	5160
CCTGTGACA	GCCCCACCCA	GCCTCACGTG	GCCACCTCTG	TCTTCCCCCA	TGAAGGGCTG	5220
GCTCCCCAGT	ATATATAAAC	CTCTCTGGAG	CTCGGGCATG	AGCCAGCAAG	GCCACCCATC	5280
CAGGCACCTC	TCAGCACACG	AGAGCTTTC	AGAGGAAGCC	TCACCAAGCC	TCTGCAATGA	5340
GGTTCTTCTG	TGCACGTGTC	TGCAGTTTG	GGCCTGAGAT	GCCAGCTGTC	CAGCTGCTGC	5400
TTCTGGCCTG	CCTGGTGTGG	GATGTGGGGG	CCAGGACAGC	TCAGCTCAGG	AAGGCCAATG	5460
ACCAGAGTGG	CCGATGCCAG	TATACCTTCA	GTGTGGCCAG	TCCCAATGAA	TCCAGCTGCC	5520
CAGACCAGAG	CCAGGCCATG	TCAGTCATCC	ATAACTTACA	GAGAGACAGC	AGCACCCAAAC	5580
GCTTAGACCT	GGAGGCCACC	AAAGCTCGAC	TCAGCTCCCT	GGAGAGCCTC	CTCCACCAAT	5640

TGACCTTGGA	CCAGGCTGCC	AGGCCCAAGG	AGACCCAGGA	GGGGCTGCAG	AGGGAGCTGG	5700
GCACCCCTGAG	GCGGGAGCGG	GACCAGCTGG	AAACCCAAAC	CAGAGAGTTG	GAGACTGCCT	5760
ACAGCAACCT	CCTCCGAGAC	AAGTCAGTTC	TGGAGGAAGA	GAAGAACGGA	CTAAGCCAAG	5820
AAAATGAGAA	TCTGGCCAGG	AGGTTGGAAA	GCAGCAGCCA	GGAGGTAGCA	AGGCTGAGAA	5880
GGGGCCAGTG	TCCCCAGACC	CGAGACACTG	CTCGGGCTGT	GCCACCAGGC	TCCAGAGAAG	5940
GTAAGAATGC	AGAGTGGGGG	GACTCTGAGT	TCAGCAGGTG	ATATGGCTCG	TAGTGACCTG	6000
CTACAGGCAC	TCCAGGCCTC	CCTGCCCTT	CTCCTAGAGA	CTGCACAGCT	AGCACAAAGAC	6060
AGATGAATTA	AGGAAAGCAC	ACGATCACCT	TCAAGTATT	CTAGTAATT	AGCTCCTGAG	6120
AGCTTCATTT	AGATTAGTGG	TTCAGAGTTC	TTGTGCCCT	CCATGTCAG		6169

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 926 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

AAGGTAGGCA	CATTGCCCTG	CAATTTATAA	TTTATGAGGT	GTTCATTAT	GGAATTGTCA	60
AATATTAACA	AAAGTAGAGA	GACTACAATG	AACTCCAATG	TAGCCATAAC	TCAGGCCAA	120
CTGTTATCAG	CACAGTCCAA	TCATGTTTA	TCTTTCCTTC	TCTGACCCCC	AACCCATCCC	180
CAGTCCTTAT	CTAAAATCAA	ATATCAAACA	CCATACTCTT	TGGGAGCCTA	TTTATTTAGT	240
TAGTTAGTTT	TCAGACAGAG	TTTCTTCTT	GTTCCAAGC	TGGAGTACAA	TAGTGTAGTC	300
TCGGCTAAC	GCAATCTCCC	CCTCCTGGT	TCAAGCAATT	CTCCTGCCTC	AGTCTCCAA	360
GAAGCTGGGA	TTATAGACAC	CTGCCACCAC	ATCCAGCTAA	TTTTTTGTG	TTTTAGAAAA	420
GACAGGGTTT	CACCATGTTG	GCCAGGCTGG	TTTCGAACCTC	CTGACCTCAG	GTGATCCGCC	480
TGCCTCGGCC	TCCCAAAGTG	CTGGGATTAC	AGGCATGAGC	CACCACGCC	GGCCGGCAGC	540
CTATTTAAAT	GTCATCCTCA	ACATAGTCAA	TCCTGGGCC	ATTTTTCTT	ACAGTAAAT	600
TTTGTCTCTT	TCTTTAATC	AGTTTCTACG	TGGAATTG	ACACTTTGGC	CTTCCAGGAA	660
CTGAAGTCCG	AGCTAACTGA	AGTTCTGCT	TCCCCAATT	TGAAGGAGAG	CCCATCTGGC	720
TATCTCAGGA	GTGGAGACGG	AGACACCGGT	ATGAAGTTAA	TTTTCTTCCC	TTTGTGCC	780
ACGTGGTCTT	TATTCACTGTC	TAGTGCTGTC	TTCAGAGAAT	CAGTATAGGG	AAATGCCCA	840
CCCAAGGGGG	AAATTAACCT	CCCTGGGAGC	AGAGGGAGGG	GAGGAGAAGA	GGAACAGAAC	900
TCTCTCTCTC	TCTCTGTTAC	CCTTGT				926

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 2099 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TGGCTCTGCC	AAGCTTCCGC	ATGATCATTG	TCTGTGTTG	GAAGATTATG	GATTAAGTGG	60
TGCTCTGTTT	TCTTTCTGAA	TTTACCAAGGA	TGTGGAGAAC	TAGTTTCCGT	AGGAGAGCCT	120
CTCACGCTGA	GAACAGCAGA	AACAATTACT	GGCAAGTATG	GTGTGTGGAT	GCGAGACCCC	180
AAGCCCACCT	ACCCCTACAC	CCAGGAGACC	ACGTGGAGAA	TCGACACAGT	TGGCACGGAT	240
GTCCGCCAGG	TTTTTGAGTA	TGACCTCATC	AGCCAGTTA	TGCAGGGCTA	CCCTTCTAAG	300
GTTCACATAC	TGCCTAGGCC	ACTGGAAAGC	ACGGGTGCTG	TGGTGTACTC	GGGGAGCCTC	360
TATTTCCAGG	GCGCTGAGTC	CAGAACTGTC	ATAAGATATG	AGCTGAATAC	CGAGACAGTG	420
AAGGCTGAGA	AGGAAATCCC	TGGAGCTGGC	TACCACGGAC	AGTTCCCGTA	TTCTTGGGTT	480
GGCTACACGG	ACATTGACTT	GGCTGTGGAT	GAAGCAGGCC	TCTGGGTAT	TTACAGCACC	540
GATGAGGCCA	AAGGTGCCAT	TGTCTCTCC	AAACTGAACC	CAGAGAATCT	GGAACCTCGAA	600

CAAACCTGGG	AGACAAACAT	CCGTAAGCAG	TCAGTCGCCA	ATGCCTTCAT	CATCTGTGGC	660
ACCTTGTACA	CCGTCAGCAG	CTACACCTCA	GCAGATGCTA	CCGTCAACTT	TGCTTATGAC	720
ACAGGCACAG	GTATCAGCAA	GACCCTGACC	ATCCCATTCA	AGAACCGCTA	TAAGTACAGC	780
AGCATGATTG	ACTACAACCC	CCTGGAGAAG	AAGCTCTTG	CCTGGGACAA	CTTGAACATG	840
GTCACTTATG	ACATCAAGCT	CTCCAAGATG	TGAAAAGCCT	CCAAGCTGTA	CAGGCAATGG	900
CAGAAGGAGA	TGCTCAGGGC	TCCTGGGGGG	AGCAGGCTGA	AGGGAGAGCC	AGCCAGCCAG	960
GGCCCAGCCA	GCTTTGACTG	CTTTCCAAGT	TTTCATTAAT	CCAGAAGGAT	GAACATGGTC	1020
ACCATCTAAC	TATTCAGGAA	TTGTAGTCTG	AGGGCGTAGA	CAATTTCATA	TAATAAATAT	1080
CCTTTATCTT	CTGTCAGCAT	TTATGGGATG	TTTAATGACA	TAGTTCAAGT	TTTCTTGTGA	1140
TTTGGGGCAA	AAGCTGTAAG	GCATAATAGT	CTTTCCCTGA	AAACCATTGC	TCTTGCATGT	1200
TACATGGTTA	CCACAAGCCA	CAATAAAAAG	CATAACTTCT	AAAGGAAGCA	GAATAGCTCC	1260
TCTGGCCAGC	ATCGAATATA	AGTAAGATGC	ATTTACTACA	GTTGGCTCT	AATGCTTCAG	1320
ATAGAATACA	GTTGGGTCTC	ACATAACCCCT	TACATTGTGA	AATAAAATT	TCTTACCCAA	1380
CGTTCTCTTC	CTTGAACCTT	GTGGGAATCT	TTGCTTAAGA	GAAGGATATA	GATTCCAACC	1440
ATCAGGTAAT	TCCCTTCAGGT	TGGGAGATGT	GATTGCAGGA	TGTTAAAGGT	GTGTGTGTGT	1500
GTGTGTGTGT	GTGTGTAAC	GAGAGGCTTG	TGCCTGGTTT	TGAGGTGCTG	CCCAGGATGA	1560
CGCCAAGCAA	ATAGCGCATC	CACACTTTCC	CACCTCCATC	TCCTGGTGCT	CTCGGCACTA	1620
CCGGAGCAAT	CTTTCCATCT	CTCCCCCTGAA	CCCACCCCTCT	ATTCACCCCTA	ACTCCACTTC	1680
AGTTTGCTTT	TGATTTTTTT	TTTTTTTTTT	TTTTTTTTTT	GAGATGGGTT	CTCGCTCTGT	1740
CACCCAGGCT	GGAGTGCAGT	GGCACGATCT	CGGCTCACTG	CAAGTTCCGC	CTCCCAGGTT	1800
CACACCATTC	TCCTGGCTCA	GCCTCCCAAG	TAGCTGGGAC	TACAGGCACC	TGCCACCACG	1860
CCTGGCTAAT	TTTTTTTTTT	TCCAGTGAAG	ATGGGTTTC	CCATGTTAGC	CAGGATGGTC	1920
TCGATCTCCT	GACCTTGTCA	TCCACCCACC	TTGGCCTCCC	AAAGTGCCTGG	GATTACAGGC	1980
GTGAGGCCACC	ACGCCCCAGCC	CCTCCACTTC	AGTTTTTATC	TGTCATCAGG	GGTATGAATT	2040
TTATAAGCCA	CACCTCAGGT	GGAGAAAGCT	TGATGCATAG	CTTGAGTATT	CTATACTGT	2099

(2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 19 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TGAGGCTTCC TCTGGAAAC

19

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

TGAAATCAGC ACACCAGTAG

20

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 21 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GCACCCATAC CCCAATAATA G

21

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AGAGTTCCCC AGATTCACC

20

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

ATCTGGGAA CTCTTCTCAG

20

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

TACAGTTGTT GCAGATACG

19

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

ACAACGTATC TGCAACAACT G

21

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

TCAGGCTTAA CTGCAGAAC

20

(2) INFORMATION FOR SEQ ID NO:14:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 19 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TTGGTTCTGC ACTTAAGCC

19

(2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 19 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

AGCAGCACAA GGGCAATCC

19

(2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 18 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

ACAGGGCTAT ATTGTGGG

18

(2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 19 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CCTGAGATGC CAGCTGTCC

19

(2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CTGAAGCATT AGAACCAAC

20

(2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

ACCTTGGACC AGGCTGCCAG

20

(2) INFORMATION FOR SEQ ID NO:20:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 19 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

AGGTTTGTTC GAGTTCCAG

19

(2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

ACAATTACTG GCAAGTATGG

20

(2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 19 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CCTTCTCAGC CTTGCTACC

19

(2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

ACACCTCAGC AGATGCTACC

20

(2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 19 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

ATGGATGACT GACATGGCC

19

(2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 19 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

AAGGATGAAC ATGGTCACC

19

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1548 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

AGAGCTTCC AGAGGAAGCC TCACCAAGCC TCTGCAATGA GGTTCTTCTG TGCACGTTGC
TGCAGCTTG GGCCTGAGAT GCCAGCTGTC CAGCTGCTGC TTCTGGCCTG CCTGGTGTGG

60

120

GATGTGGGGG	CCAGGACAGC	TCAGCTCAGG	AAGGCCAATG	ACCAGAGTGG	CCGATGCCAG	180
TATACCTTCA	GTGTGGCCAG	TCCCATTGAA	TCCAGCTGCC	CAGAGCAGAG	CCAGGCCATG	240
TCAGTCATCC	ATAACTTACA	GAGAGACAGC	AGCACCCAAAC	GCTTAGACCT	GGAGGCCACC	300
AAAGCTCGAC	TCAGCTCCCT	GGAGAGCCTC	CTCCACCAAT	TGACCTTGGA	CCAGGCTGCC	360
AGGCCCCAGG	AGACCAGGA	GGGGCTGCAG	AGGGAGCTGG	GCACCCCTGAG	GCGGGAGCGG	420
GACCAGCTGG	AAACCCAAAC	CAGAGAGTTC	GAGACTGCCT	ACAGCAACCT	CCTCCGAGAC	480
AAGTCAGTTTC	TGGAGGAAGA	GAAGAACCGA	CTAAGGCAAG	AAAATGAGAA	TCTGGCCAGG	540
AGGTTGGAAA	GCAGCAGCCA	GGAGGTAGCA	AGGCTGAGAA	GGGGCCAGTG	TCCCCAGACC	600
CGAGACACTG	CTCGGGCTGT	GCCACCAGGC	TCCAGAGAAG	TTTCTACGTG	GAATTGGAC	660
ACTTTGGCCT	TCCAGGAAC	GAAGTCCGAG	CTAACTGAAG	TTCCCTGCTTC	CCGAATTGG	720
AAGGAGAGCC	CATCTGGCTA	TCTCAGGAGT	GGAGAGGGAG	ACACCGGATG	TGGAGAACTA	780
GTTTGGGTAG	GAGAGCCTCT	CACGCTGAGA	ACAGCAGAAA	CAATTACTGG	CAAGTATGGT	840
GTGTGGATGC	GAGACCCAA	GCCCACCTAC	CCCTACACCC	AGGAGACCAC	GTGGAGAATC	900
GACACAGTTG	GCACGGATGT	CCGCCAGGTT	TTTGTAGTATG	ACCTCATCAG	CCAGTTTATG	960
CAGGGCTACC	CTTCTAAGGT	TCACATACTG	CCTAGGCCAC	TGGAAAGCAC	GGGTGCTGTG	1020
GTGTACTCGG	GGAGCCTCTA	TTTCCAGGGC	GCTGAGTCCA	GAACGTGAT	AAGATATGAG	1080
CTGAATACCG	AGACAGTGAA	GGCTGAGAAG	GAAATCCCTG	GAGCTGGCTA	CCACGGACAG	1140
TTCCCGTATT	CTTGGGTGG	CTACACGGAC	ATTGACTTGG	CTGTGGATGA	AGCAGGCCTC	1200
TGGGTCACTT	ACAGCACCAGA	TGAGGCCAAA	GGTGCCATTG	TCCTCTCCAA	ACTGAACCCA	1260
GAGAATCTGG	AACTCGAAC	AACCTGGGAG	ACAAACATCC	GTAAGCAGTC	AGTCGCCAAT	1320
GCCTTCATCA	TCTGTGGCAC	CTTGTACACC	GTCAGCAGCT	ACACCTCAGC	AGATGCTACC	1380
GTCAACTTTG	CTTATGACAC	AGGCACAGGT	ATCAGCAAGA	CCCTGACCAT	CCCATTCAAG	1440
AACCGCTATA	AGTACAGCAG	CATGATTGAC	TACAACCCCC	TGGAGAAGAA	GCTCTTGCC	1500
TGGGACAAC	TGAACATGGT	CACTTATGAC	ATCAAGCTCT	CCAAGATG		1548

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 178 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Thr Gly Ala Val Val Tyr Ser Gly Ser Leu Tyr Phe Gln Gly Ala Glu
 1 5 10 15
 Ser Arg Thr Val Ile Arg Tyr Glu Leu Asn Thr Glu Thr Val Lys Ala
 20 25 30
 Glu Lys Glu Ile Pro Gly Ala Gly Tyr His Gly Gln Phe Pro Tyr Ser
 35 40 45
 Trp Gly Gly Tyr Thr Asp Ile Asp Leu Ala Val Asp Glu Ala Gly Leu
 50 55 60
 Trp Val Ile Tyr Ser Thr Asp Glu Ala Lys Gly Ala Ile Val Leu Ser
 65 70 75 80
 Lys Leu Asn Pro Glu Asn Leu Glu Leu Glu Gln Thr Trp Glu Thr Asn
 85 90 95
 Ile Arg Lys Gln Ser Val Ala Asn Ala Phe Ile Ile Cys Gly Thr Leu
 100 105 110
 Tyr Thr Val Ser Ser Tyr Thr Ser Ala Asp Ala Thr Val Asn Phe Ala
 115 120 125
 Tyr Asp Thr Gly Thr Gly Ile Ser Lys Thr Leu Thr Ile Pro Phe Lys
 130 135 140
 Asn Arg Tyr Lys Tyr Ser Ser Met Ile Asp Tyr Asn Pro Leu Glu Lys
 145 150 155 160
 Lys Leu Phe Ala Trp Asp Asn Leu Asn Met Val Thr Tyr Asp Ile Lys
 165 170 175
 Leu Ser

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 131 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Arg	Phe	Asp	Leu	Lys	Thr	Glu	Thr	Ile	Leu	Lys	Thr	Arg	Ser	Leu	Asp
1						5			10			15			
Tyr	Ala	Gly	Tyr	Asn	Asn	Met	Tyr	His	Tyr	Ala	Trp	Gly	Gly	His	Ser
						20			25			30			
Asp	Ile	Asp	Leu	Met	Val	Asp	Glu	Ser	Gly	Leu	Trp	Ala	Val	Tyr	Ala
						35			40			45			
Thr	Asn	Gln	Asn	Ala	Gly	Asn	Ile	Val	Val	Ser	Arg	Leu	Asp	Pro	Val
						50			55			60			
Ser	Leu	Gln	Thr	Leu	Gln	Thr	Trp	Asn	Thr	Ser	Tyr	Pro	Lys	Arg	Xaa
						65			70			75			80
Pro	Gly	Xaa	Ala	Phe	Ile	Ile	Cys	Gly	Thr	Cys	Tyr	Val	Thr	Asn	Gly
						85			90			95			
Tyr	Ser	Gly	Gly	Thr	Lys	Val	His	Tyr	Ala	Tyr	Gln	Thr	Asn	Ala	Ser
						100			105			110			
Thr	Tyr	Glu	Tyr	Ile	Asp	Ile	Pro	Phe	Gln	Asn	Lys	Leu	Xaa	Pro	His
						115			120			125			
Phe	Pro	Cys													
		130													

(2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 178 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Gly	Thr	Gly	Gln	Val	Val	Tyr	Asn	Gly	Ser	Ile	Tyr	Phe	Asn	Lys	Phe
1						5			10			15			
Gln	Ser	His	Ile	Ile	Ile	Arg	Phe	Asp	Leu	Lys	Thr	Glu	Thr	Ile	Leu
						20			25			30			
Lys	Thr	Arg	Ser	Leu	Asp	Tyr	Ala	Gly	Tyr	Asn	Asn	Met	Tyr	His	Tyr
						35			40			45			
Ala	Trp	Gly	Gly	His	Ser	Asp	Ile	Asp	Leu	Met	Val	Asp	Glu	Asn	Gly
						50			55			60			
Leu	Trp	Ala	Val	Tyr	Ala	Thr	Asn	Gln	Asn	Ala	Gly	Asn	Ile	Val	Ile..
						65			70			75			80
Ser	Lys	Leu	Asp	Pro	Val	Ser	Leu	Gln	Ile	Leu	Gln	Thr	Trp	Asn	Thr
						85			90			95			
Ser	Tyr	Pro	Lys	Arg	Ser	Ala	Gly	Glu	Ala	Phe	Ile	Ile	Cys	Gly	Thr
						100			105			110			
Leu	Tyr	Val	Thr	Asn	Gly	Tyr	Ser	Gly	Gly	Thr	Lys	Val	His	Tyr	Ala

115	120	125
Tyr Gln Thr Asn Ala Ser Thr Tyr Glu Tyr Ile Asp Ile Pro Phe Gln		
130	135	140
Asn Lys Tyr Ser His Ile Ser Met Leu Asp Tyr Asn Pro Lys Asp Arg		
145	150	155
Ala Leu Tyr Ala Trp Asn Asn Gly His Gln Thr Leu Tyr Asn Val Thr		160
165	170	175
Leu Phe		

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 177 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Gly Ala Gly Val Val Val His Asn Asn Asn Leu Tyr Tyr Asn Cys Phe			
1	5	10	15
Asn Ser His Asp Met Cys Arg Ala Ser Leu Thr Ser Gly Val Tyr Gln			
20	25	30	
Lys Lys Pro Leu Leu Asn Ala Leu Phe Asn Asn Arg Phe Ser Tyr Ala			
35	40	45	
Gly Thr Met Phe Gln Asp Met Asp Phe Ser Ser Asp Glu Lys Gly Leu			
50	55	60	
Trp Val Ile Phe Thr Thr Glu Lys Ser Ala Gly Lys Ile Val Val Gly			
65	70	75	80
Lys Val Asn Val Ala Thr Phe Thr Val Asp Asn Ile Trp Ile Thr Thr			
85	90	95	
Gln Asn Lys Ser Asp Ala Ser Asn Ala Phe Met Ile Cys Gly Val Leu			
100	105	110	
Tyr Val Thr Arg Ser Leu Gly Pro Lys Met Glu Glu Val Phe Tyr Met			
115	120	125	
Phe Asp Thr Lys Thr Gly Lys Glu Gly His Leu Ser Ile Met Met Glu			
130	135	140	
Lys Met Ala Glu Lys Val His Ser Leu Ser Tyr Asn Ser Asn Asp Arg			
145	150	155	160
Lys Leu Tyr Met Phe Ser Glu Gly Tyr Leu Leu His Tyr Asp Ile Ala			
165	170	175	
Leu			

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 74 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Gly Val Val Tyr Ser Arg Leu Thr Glu Thr Leu Ala Gly Tyr Asn Asn

1	5	10	15
Tyr Ala Trp Gly Gly Asp Ile Asp Leu Val Asp Glu Gly Leu Trp Tyr			
20	25	30	
Thr Ala Gly Ile Val Ser Lys Leu Pro Leu Gln Thr Trp Thr Lys Ala			
35	40	45	
Phe Ile Ile Cys Gly Thr Leu Tyr Val Thr Tyr Val Tyr Ala Tyr Thr			
50	55	60	
Ile Tyr Asp Tyr Asn Pro Lys Leu Tyr Leu			
65	70		

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 504 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met Arg Phe Phe Cys Ala Arg Cys Cys Ser Phe Gly Pro Glu Met Pro			
1	5	10	15
Ala Val Gln Leu Leu Leu Ala Cys Leu Val Trp Asp Val Gly Ala			
20	25	30	
Arg Thr Ala Gln Leu Arg Lys Ala Asn Asp Gln Ser Gly Arg Cys Gln			
35	40	45	
Tyr Thr Phe Ser Val Ala Ser Pro Asn Glu Ser Ser Cys Pro Glu Gln			
50	55	60	
Ser Gln Ala Met Ser Val Ile His Asn Leu Gln Arg Asp Ser Ser Thr			
65	70	75	80
Gln Arg Leu Asp Leu Glu Ala Thr Lys Ala Arg Leu Ser Ser Leu Glu			
85	90	95	
Ser Leu Leu His Gln Leu Thr Leu Asp Gln Ala Ala Arg Pro Gln Glu			
100	105	110	
Thr Gln Glu Gly Leu Gln Arg Glu Leu Gly Thr Leu Arg Arg Glu Arg			
115	120	125	
Asp Gln Leu Glu Thr Gln Thr Arg Glu Leu Glu Thr Ala Tyr Ser Asn			
130	135	140	
Leu Leu Arg Asp Lys Ser Val Leu Glu Glu Lys Lys Arg Leu Arg			
145	150	155	160
Gln Glu Asn Glu Asn Leu Ala Arg Arg Leu Glu Ser Ser Gln Glu			
165	170	175	
Val Ala Arg Leu Arg Arg Gly Gln Cys Pro Gln Thr Arg Asp Thr Ala			
180	185	190	
Arg Ala Val Pro Pro Gly Ser Arg Glu Val Ser Thr Trp Asn Leu Asp			
195	200	205	
Thr Leu Ala Phe Gln Glu Leu Lys Ser Glu Leu Thr Glu Val Pro Ala			
210	215	220	
Ser Arg Ile Leu Lys Glu Ser Pro Ser Gly Tyr Leu Arg Ser Gly Glu			
225	230	235	240
Gly Asp Thr Gly Cys Gly Glu Leu Val Trp Val Gly Glu Pro Leu Thr			
245	250	255	
Leu Arg Thr Ala Glu Thr Ile Thr Gly Lys Tyr Gly Val Trp Met Arg			
260	265	270	
Asp Pro Lys Pro Thr Tyr Pro Tyr Thr Gln Glu Thr Thr Trp Arg Ile			
275	280	285	
Asp Thr Val Gly Thr Asp Val Arg Gln Val Phe Glu Tyr Asp Leu Ile			

290 Ser Gln Phe Met Gln Gly Tyr Pro Ser Lys Val His Ile Leu Pro Arg 305 Pro Leu Glu Ser Thr Gly Ala Val Val Tyr Ser Gly Ser Leu Tyr Phe 325 Gln Gly Ala Glu Ser Arg Thr Val Ile Arg Tyr Glu Leu Asn Thr Glu 340 Thr Val Lys Ala Glu Lys Glu Ile Pro Gly Ala Gly Tyr His Gly Gln 355 Phe Pro Tyr Ser Trp Gly Gly Tyr Thr Asp Ile Asp Leu Ala Val Asp 370 Glu Ala Gly Leu Trp Val Ile Tyr Ser Thr Asp Glu Ala Lys Gly Ala 385 Ile Val Leu Ser Lys Leu Asn Pro Glu Asn Leu Glu Leu Glu Gln Thr 405 Trp Glu Thr Asn Ile Arg Lys Gln Ser Val Ala Asn Ala Phe Ile Ile 420 Cys Gly Thr Leu Tyr Thr Val Ser Ser Tyr Thr Ser Ala Asp Ala Thr 435 Val Asn Phe Ala Tyr Asp Thr Gly Thr Gly Ile Ser Lys Thr Leu Thr 450 Ile Pro Phe Lys Asn Arg Tyr Lys Tyr Ser Ser Met Ile Asp Tyr Asn 465 Pro Leu Glu Lys Lys Leu Phe Ala Trp Asp Asn Leu Asn Met Val Thr 485 Tyr Asp Ile Lys Leu Ser Lys Met 500	295 310 315 330 345 350 360 365 375 380 390 395 410 415 425 430 440 445 455 460 470 475 490 495	300 320 335 350 365 380 400 415 430 445 460 480 495
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WHAT IS CLAIMED IS:

1. A method for diagnosing glaucoma in a patient which comprises the steps:
 - (A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said first marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that specifically hybridizes to a polynucleotide that is linked to a TIGR promoter, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule, and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting TIGR response in said patient;
 - (B) permitting hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and
 - (C) detecting the presence of said polymorphism, wherein the detection of said polymorphism is diagnostic of glaucoma.
2. A method for diagnosing glaucoma in a patient according to claim 1, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt1*.
3. A method for diagnosing glaucoma in a patient according to claim 1, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt2*.
4. A method for diagnosing glaucoma in a patient according to claim 1, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt3*.
5. A method for diagnosing glaucoma in a patient according to claim 1, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt4*.
6. A method for diagnosing glaucoma in a patient according to claim 1, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt5*.
7. A method for diagnosing glaucoma in a patient according to claim 1, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRsv1*.
8. A method for diagnosing glaucoma in a patient according to claim 1, further comprising a second marker nucleic acid molecule.
9. A method for diagnosing glaucoma in a patient according to claim 8, wherein said first marker nucleic acid molecule and said second marker nucleic acid molecule are selected from the group consisting of a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9, a nucleic acid

molecule that comprises the sequence of SEQ ID NO: 10, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 11, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 14, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 15, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 16, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 17, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 19, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 20, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 21, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 22, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 23, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 24 and a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.

10. A method for diagnosing glaucoma in a patient according to claim 9, wherein said first marker nucleic acid molecule and said second marker nucleic acid molecule are selected from the group consisting of a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18, and a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25

11. A method for diagnosing glaucoma in a patient according to claim 10, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12.

12. A method for diagnosing glaucoma in a patient according to claim 10, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8.

13. A method for diagnosing glaucoma in a patient according to claim 10, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6.

14. A method for diagnosing glaucoma in a patient according to claim 10, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.

15. A method for diagnosing steroid sensitivity in a patient which comprises the steps:

(A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that is linked to a TIGR promoter, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule, and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting TIGR response in said patient;

(B) permitting hybridization between said TIGR-encoding marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and

(C) detecting the presence of said polymorphism, wherein the detection of said polymorphism is diagnostic of steroid sensitivity.

16. A method for diagnosing steroid sensitivity in a patient according to claim 15, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt1*.

17. A method for diagnosing steroid sensitivity in a patient according to claim 15, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt2*.

18. A method for diagnosing steroid sensitivity in a patient according to claim 15, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt3*.

19. A method for diagnosing steroid sensitivity in a patient according to claim 15, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt4*.

20. A method for diagnosing steroid sensitivity in a patient according to claim 15, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt5*.

21. A method for diagnosing steroid sensitivity in a patient according to claim 15, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRsv1*.

22. A method for diagnosing steroid sensitivity in a patient according to claim 15, further comprising a second marker nucleic acid molecule.

23. A method for diagnosing steroid sensitivity in a patient according to claim 22, wherein said first marker nucleic acid molecule and said second marker nucleic acid molecule are selected from the group consisting of a nucleic acid molecule that

comprises the sequence of SEQ ID NO: 6, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 10, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 11, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 14, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 15, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 16, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 17, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 19, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 20, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 21, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 22, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 23, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 24 and a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.

24. A method for diagnosing steroid sensitivity in a patient according to claim 23, wherein said first marker nucleic acid molecule and said second marker nucleic acid molecule are selected from the group consisting of a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18, and a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.

25. A method for diagnosing steroid sensitivity in a patient according to claim 24, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12.

26. A method for diagnosing glaucoma in a patient according to claim 24, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 5.

27. A method for diagnosing steroid sensitivity in a patient according to claim 24, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6.
28. A method for diagnosing steroid sensitivity in a patient according to claim 24, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.
29. The method of claims 10 or 24, wherein said complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient has been amplified using a nucleic acid amplification method.
30. The method of claim 1, wherein said marker nucleic acid molecule is selected from the group consisting of D1S2536 marker nucleic acid, D1S210 marker nucleic acid, D1S1552 marker nucleic acid, D1S2536 marker nucleic acid D1S2790 marker nucleic acid, SHGC-12820 marker nucleic acid, and D1S2558 marker nucleic acid.
31. The method of claim 30, wherein said marker nucleic acid molecule is D1S2536 marker nucleic acid.
32. The method of claim 15, wherein said marker nucleic acid molecule is selected from the group consisting of D1S2536 marker nucleic acid, D1S210 marker nucleic acid, D1S1552 marker nucleic acid, D1S2536 marker nucleic acid D1S2790 marker nucleic acid, SHGC-12820 marker nucleic acid, and D1S2558 marker nucleic acid.
33. The method of claim 32, wherein said marker nucleic acid molecule is D1S2536 marker nucleic acid.
34. A nucleic acid molecule that comprises the sequence of SEQ ID NO: 1.
35. A recombinant DNA molecule containing a polynucleotide that specifically hybridizes to SEQ ID NO: 1.
36. A substantially purified molecule that specifically binds to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 1.
37. A nucleic acid molecule that comprises the sequence of SEQ ID NO: 3.
38. A recombinant DNA molecule containing a polynucleotide that specifically hybridizes to SEQ ID NO: 3.
39. A substantially purified molecule that specifically binds to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 3.
40. A nucleic acid molecule that comprises the sequence of SEQ ID NO: 4.
41. A recombinant DNA molecule containing a polynucleotide that specifically hybridizes to SEQ ID NO: 4.

42. A substantially purified molecule that specifically binds to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 4.
43. A nucleic acid molecule that comprises the sequence of SEQ ID NO: 5.
44. A recombinant DNA molecule containing a polynucleotide that specifically hybridizes to SEQ ID NO: 5.
45. A substantially purified molecule that specifically binds to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 5.
46. A nucleic acid molecule that comprises the sequence of SEQ ID NO: 26.
47. A recombinant DNA molecule containing a polynucleotide that specifically hybridizes to SEQ ID NO: 26.
48. A substantially purified molecule that specifically binds to a nucleic acid molecule that comprises the sequence of SEQ ID NO: 26.
49. A substantially purified molecule that specifically binds to a nucleic acid molecule selected from the group consisting of a nucleic acid molecule that comprises a *cis* element characteristic of PRL-FP111, a nucleic acid molecule that comprises a glucocorticoid response *cis* element, a nucleic acid molecule that comprises a *cis* element characteristic of GR/PR, a nucleic acid molecule that comprises a shear stress response *cis* element, a nucleic acid molecule that comprises a glucocorticoid response *cis* element, a nucleic acid molecule that comprises a *cis* element characteristic of CBE, a nucleic acid molecule that comprises a *cis* element capable of binding NFE, a nucleic acid molecule that comprises a *cis* element capable of binding KTF.1-CS, a nucleic acid molecule that comprises a *cis* element characteristic of PRE, a nucleic acid molecule that comprises a *cis* element characteristic of ETF-EGFR, a nucleic acid molecule that comprises a *cis* element capable of binding SRE-cFos, a nucleic acid molecule that comprises a *cis* element characteristic of Alu, a nucleic acid molecule that comprises a *cis* element capable of binding VBP, a nucleic acid molecule that comprises a *cis* element characteristic of Malt-CS, a nucleic acid molecule that comprises a *cis* element capable of binding ERE, a nucleic acid molecule that comprises a *cis* element characteristic of NF-mutagen, a nucleic acid molecule that comprises a *cis* element capable of binding myc-PRF, a nucleic acid molecule that comprises a *cis* element capable of binding AP2, a nucleic acid molecule that comprises a *cis* element capable of binding HSTF, a nucleic acid molecule that comprises a *cis* element characteristic of SBF, a nucleic acid molecule that comprises a *cis* element capable of binding NF-1, a nucleic acid molecule that comprises a *cis* element capable of binding NF-MHCIIA/B, a nucleic acid molecule that comprises a *cis* element capable of binding PEA1, a nucleic acid molecule that comprises a *cis* element characteristic of ICS, a nucleic acid molecule

that comprises a *cis* element capable of binding ISGF2, a nucleic acid molecule that comprises a *cis* element capable of binding zinc, a nucleic acid molecule that comprises a *cis* element characteristic of CAP/CRP-galO, a nucleic acid molecule that comprises a *cis* element capable of binding AP1, a nucleic acid molecule that comprises a *cis* element capable of binding SRY, , a nucleic acid molecule that comprises a *cis* element characteristic of GC2, a nucleic acid molecule that comprises a *cis* element capable of binding PEA3, a nucleic acid molecule that comprises a *cis* element characteristic of MIR, a nucleic acid molecule that comprises a *cis* element capable of binding NF-HNF-1, a nucleic acid molecule that comprises a thyroid receptor *cis* element, and a nucleic acid molecule that comprises a *cis* element capable of binding NFkB.

50. A method of treating glaucoma which comprises administering to a glaucomatous patient an effective amount of an agent capable of binding a *cis* element located within SEQ ID NO: 1.

51. The method of claim 50, wherein said agent inhibits the expression of a TIGR mRNA.

52. The method of claim 50, wherein said agent binds a DNA sequence within SEQ ID NO: 1.

53. The method of claim 50, wherein said agent binds a nucleic acid molecule that comprises a *cis* element characteristic of PRL-FP111, a nucleic acid molecule that comprises a glucocorticoid response *cis* element, a nucleic acid molecule that comprises a *cis* element characteristic of GR/PR, a nucleic acid molecule that comprises a shear stress response *cis* element, a nucleic acid molecule that comprises a glucocorticoid response *cis* element, a nucleic acid molecule that comprises a *cis* element characteristic of CBE, a nucleic acid molecule that comprises a *cis* element capable of binding NFE, a nucleic acid molecule that comprises a *cis* element capable of binding KTF.1-CS, a nucleic acid molecule that comprises a *cis* element characteristic of PRE, a nucleic acid molecule that comprises a *cis* element characteristic of ETF-EGFR, a nucleic acid molecule that comprises a *cis* element capable of binding SRE-cFos, a nucleic acid molecule that comprises a *cis* element characteristic of Alu, a nucleic acid molecule that comprises a *cis* element capable of binding VBP, a nucleic acid molecule that comprises a *cis* element characteristic of Malt-CS, a nucleic acid molecule that comprises a *cis* element capable of binding ERE, a nucleic acid molecule that comprises a *cis* element characteristic of NF-mutagen, a nucleic acid molecule that comprises a *cis* element capable of binding myc-PRF, a nucleic acid molecule that comprises a *cis* element capable of binding AP2, a nucleic acid molecule that comprises a *cis* element capable of binding HSTF, a nucleic acid molecule that comprises a *cis* element characteristic of

SBF, a nucleic acid molecule that comprises a *cis* element capable of binding NF-1, a nucleic acid molecule that comprises a *cis* element capable of binding NF-MHCIIA/B, a nucleic acid molecule that comprises a *cis* element capable of binding PEA1, a nucleic acid molecule that comprises a *cis* element characteristic of ICS, a nucleic acid molecule that comprises a *cis* element capable of binding ISGF2, a nucleic acid molecule that comprises a *cis* element capable of binding zinc, a nucleic acid molecule that comprises a *cis* element characteristic of CAP/CRP-galO, a nucleic acid molecule that comprises a *cis* element capable of binding AP1, a nucleic acid molecule that comprises a *cis* element capable of binding SRY, a nucleic acid molecule that comprises a *cis* element characteristic of GC2, a nucleic acid molecule that comprises a *cis* element capable of binding PEA3, a nucleic acid molecule that comprises a *cis* element characteristic of MIR, a nucleic acid molecule that comprises a *cis* element capable of binding NF-HNF-1, a nucleic acid molecule that comprises a thyroid receptor *cis* element, and a nucleic acid molecule that comprises a *cis* element capable of binding NF κ B.

54. A method for prognosing glaucoma in a patient which comprises the steps:

(A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said first marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that specifically hybridizes to a polynucleotide that is linked to a TIGR promoter, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule, and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting TIGR response in said patient;

(B) permitting hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and

(C) detecting the presence of said polymorphism, wherein the detection of said polymorphism is prognostic of glaucoma.

55. A method for prognosing glaucoma in a patient according to claim 54, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt1*.

56. A method for prognosing glaucoma in a patient according to claim 54, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt2*.

57. A method for prognosing glaucoma in a patient according to claim 54, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt3*.

58. A method for prognosing glaucoma in a patient according to claim 54, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt4*.

59. A method for prognosing glaucoma in a patient according to claim 54, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRmt5*.
60. A method for prognosing glaucoma in a patient according to claim 54, wherein said marker nucleic acid molecule is capable of specifically detecting *TIGRsv1*.
61. A method for prognosing glaucoma in a patient according to claim 54, further comprising a second marker nucleic acid molecule.
62. A method for prognosing glaucoma in a patient according to claim 61, wherein said first marker nucleic acid molecule and said second marker nucleic acid molecule are selected from the group consisting of a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 10, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 11, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 14, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 15, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 16, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 17, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 19, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 20, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 21, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 22, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 23, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 24 and a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.
63. A method for diagnosing glaucoma in a patient according to claim 62, wherein said first marker nucleic acid molecule and said second marker nucleic acid molecule are selected from the group consisting of a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13, a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18, and a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25

64. A method for diagnosing glaucoma in a patient according to claim 63, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 13 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 12.
65. A method for diagnosing glaucoma in a patient according to claim 63, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 9 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 8.
66. A method for diagnosing glaucoma in a patient according to claim 63, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 7 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 6.
67. A method for diagnosing glaucoma in a patient according to claim 63, wherein said first marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 18 and said second marker nucleic acid molecule is a nucleic acid molecule that comprises the sequence of SEQ ID NO: 25.
68. The method of claim 54, wherein said marker nucleic acid molecule is selected from the group consisting of D1S2536 marker nucleic acid, D1S210 marker nucleic acid, D1S1552 marker nucleic acid, D1S2536 marker nucleic acid D1S2790 marker nucleic acid, SHGC-12820 marker nucleic acid, and D1S2558 marker nucleic acid.
69. The method of claim 68, wherein said marker nucleic acid molecule is D1S2536 marker nucleic acid.

1	ATC TTTGTCAGT TTACCTCAGG GCTATTATGA	33
34	AATGAAATGA GATAACCAAT GTGAAAGTCC TATAAACTGT ATAGCCTCCA TTGGATGTA	93
94	TGTCTTGGC AGGATGATAA AGAACATCAGGA AGAAGGAGTA TCCACGTTAG CCAAGTGTCC	153
154	AGGCTGTGTC TGCTCTTATT TTAGTGACAG ATGTTGCTCC TGACAGAACG TATTCTTCAG	213
214	GAAACATCAC ATCCAATATG GTAAATCCAT CAACACGGAG CTAGAAACG GGAATGAGAT	273
274	GGGCACCTGC CCAAGGAAA ATGCCAGGAG AGCAATAAT GATGAAATAAT AAACCTTTCC	333
334	CTTTGTTTT AATTCAGGA AAAATGATG AGGACAAAAA TCATGATA AGGAAACAG (PrL.FPIII) CCTG AATGATA AGAA	393
394	CTCAGLAAA AGATGTTCC AAATTGGTA TAAAGTATTT GTCCTGGG AACGACCTC (PR/GP-MMTV) T GTCTTTTGG AA (SSRE) CGACCC	453
454	CATGTGAGCT TGATGGAAA ATGGGAAAAA CGTCAAAAGC ATGATCTGAT CAGATCCCIA	513
514	AGTGGATTAT TATTTTAAA ACCAGATGGC ATCCTCTGG GGAGGCAAGT TCAGGAAGGT	573
574	CATGTTAGCA LAGGACATTA CAATCACAGC AAAATCAAAA TTCCGAAAT GGAGGAGGAA CCTTTAG-A LAGGACAAA CAGAATG (nGRE-PRL)	633
634	AATGGGACT GGGAAAGCTT TCATAACAGT GATTAGGCAG TTGACCATGT TCGAACACC	693
694	TCCCCGTCTA TACCAAGGAA CACAAAATT GACTGGCTA AGCTGGACT TTCAAGGAA GGCTGGACT GTC (CBE-P53)	753
754	ATATGAAAAA CTGAGAGCAA AACAAAAGAC ATGGTAAA GGCAACCAGA ACATTGTGAG ATTTTCTGA TTGGTAAA GT (NFEI)	813
814	CCTTCAAAGC AGCAGTGCC CTCAGCAGGG ACCCTGAGGC ATTTGCCTTT AGGAAGGCCA G ACCCTGAGGC T (KTF.1-CS)	873
874	GTTCCTTAA GGAATCTTAA GAAACTCTTG AAGATCATG AATTTAACCC ATTTTAAGTA	933
934	TAAAACAAAT ATGCGATGCA TAATCAGTTT AGACATGGGT CCCATTTTA TAAAGTCAGG (PRE-lysotyme) AGCCGT	993
994	CATACAAGGA TAACGTGTCC CAGCTCCGGA TAGGTCTAGAA ATCAATTAGAA ATCACTGTGT GATCCTAGGA GCAGAAAGTTC CAGCTATGGT CAG (GRE-hMT:GG TACACTGTGT	1053
1054	CCCCATCCTA ACTTTTCAG AATGATCTGT CATAGCCCTC ACACACAGGC CCGATGTGTC CCT	1113
1114	TGACCTACAA CCACATCTAC AACCCAAAGTG CCTCAACCAT TCTAACGTG TCATCTCAGT	1173

FIGURE 1A

1174	AGGTCCCATT ACAAAATGCCA CCTCCCCGTG GCAGCCCATC CGCGTCCACCA GGAAGTCCTCC	1233
1234	CCACTCTAGA CTTCTGCATC ACGATGTTAC AGCCAGAAC TCCGTGAGGG TGAGGGATCG (SSRE) GATTC	1293
1294	TGTCTTACAC CTACCTGTAT GETCTACACC TGAGCTCAGT GC3ACCTCTG CCTCCCCGGT	1353
1354	<u>TC3AGCAATT CTCCAGTC</u> AGCCCTGGGA CTACAGGCGC ACGCCGGGT c AGCCCTGGGA CTACAGGCGC ACGCCGGGT (ETP, EGFR)	1413
1414	<u>AATTTTGTA TGTGTAGTAG AGATGGGGTT TCACCATATT AGCCGGCTG GTCTTGAAC</u> Alu Repeat Region ccatatt AGG (SRE-cFos)	1473
1474	<u>CCAGACCTCA GGTCATCCAC CCACCTCAGC CTCCCTAAGT GCGGGATTA CAGGCATGAG</u>	1533
1534	<u>TCACCGCGCC CGGGCAAGGG TCAGTGTATA ATAAAGGATA ACTTGAATGG TTTACTAAC</u>	1593
1594	CAACAGGGAA ACAGACAAA GCTGTGATAA TTTCAGGGAT TCTTGGGATG GGGAAATGGTG	1653
1654	CCATGAGCTG CCTGCCTAGT CCCAGACCAC TGGTCCTCAT CACTTTCTTC CCTCATCCTC	1713
1714	ATTTTCAGGC TAAGTTACCA TTTTATTACAC CATGCTTTTG TGGTAAGCCT CCACATCGTT	1773
1774	ACTGAAATAA GAGTATACAT AAATAGTTTC CTTTTGGGGC CTTCTGTGTG TGTGTATAGG GGTATACAT AAC (VBP-vitel)	1833
1834	GGAGGAGGGC ATACCCAGA GACTCCTTGA AGCCCCGGC AGAGGTTTCC TCTCCAGCTG ggakgacc (MALT-CS)	1893
1894	GGGGAGCCCT GCAAGCACCC GGGGTCTGG GTGTCTGAG CAACCTGCCA GCCCGTGCCA	1953
1954	CTGGTTGTT TGTTATCACT CTCTAGGGAC CTGTTGCTTT CTATTTCTGT GTGACTCGTT	2013
2014	CATTCACTCCA GGCAATTATT GACAATTAT TGAGTACTTA TATCTGCCAG ACACCAAGAGA	2073
2074	CAAAATGGTG AGCRAAGCAG TCACCTGCCCT ACCTTCGTGG AGGTGACAGT TTCTCATGGA	2133
2134	AGACGTGCAG AAGAAAATTA ATAGCCAGCC AACTTAAACC CAGTGTGAA AGAAAGGAA GCGTGAC CGGAGCTGAA AGAAAGGAAAC	2193
2194	TAAACACCAT CTTGAAGAAT TGTGCGCAGC ATCCCTTAC AAGGCCACCT CCCTAGCGCC AC (ERB-c.vitel)	2253
2254	CCCTGCTGCC TCCATCGTGC CCGGAGGCCCG CCAAGCCCCA GTCTTCCAG CCTCCTCCTC	2313
2314	CATCAGTCAC AGCGCTGCAG CTGGCTGCC TCGCTTCCCG TGAATCGTCC TGGTCCATCT AGCGAC CTGGC (NF-mutagen)	2373
2374	GAGCTGGAGA CCTCCTGGCT CCAGGCTCCA GAAAGGAAAT GAGGAGGGAA ACTAGTCTAA A GAAAGGAAAG GGA (PREF-myc)	2433
2434	CGGAGAAATCT GGAGGGGACG GTCTTCTTC AGAGGGAAAG GGGCCTCCAC GTCCAGGAGA ACCCGGTACA CTGTGCTTC CCGCT (GRE-hmt.IIa) CC CTTGGGCCA ATGTGCTG AGGGGA (GRE-EGR)	2493

FIGURE 1B

2494	ATTCAGGAG GTGGGGACTG CAGGGAGT GG ACC C ^T TGG AGGGGG TGCTGAAGG CTGG GG GCGCTGG GA (AP.2-SV40)	2553
2554	CAGGAAGGTG AAAAGGGCAA GGCTGAAGCT GCCCAGATGT TCAGTGTGTGTCACGGGGCT	2613
2614	GGGAGTTTC CGTTGCTTC TGAGGCTT TTTATCTTT CTCTGCTTGG AGGAGAAGAA CT CGTTGCTTCG AG (ESTY-hsp70)	2673
2674	GTCTATTCA TGAAGGGATG CAGTTICATA AAGTCAGCTG TTA AA ATTCC AGGGTGTGCA A	2733
2734	TCGTTTCC TTCACGAAGG CCTTTATTAA ATGGGAATAT AGGAAGCGAG CTCATTTCCT TGGTTTIG (SBF.yeast)	2793
2794	AGGCCGTTAA TTCACGAAG AAGTGACTGG AGTCTTTCT TTCA T GTCTT CTGGGCACT	2853
2854	ACTCAGCCCT GTGGTGGACT TGGCTTATGC AAGACGGCTG AA A CTTGG AATCAGGAGA	2913
2914	CTCGGTTTC TTCTGGTTT TCCCATTGGT TGGCTGTGCG ACCGTGGGCA AGTGTCTCTC C TTCTGGTTT TGCAG (NF.1-bithorax) (NF-MECII/1) CCA T GGT T	2973
2974	CTTCCCTGGG CCATAGTCTT CTCTGCTATA AAGACCTTG CAGCTCTCGT GTTCTGTGAA	3033
3034	CACTCCCTG TGATTCTCTG TGAGGGGGGA TGTGAGAGG GGAAGGAGGC AGAGCTGGAG	3093
3094	CAGCTGAGCC ACAGGGGAGG TGGAGGGGGGA CAGGAAGGC A GGCAGAAGCT GGGTGTCCA	3153
3154	TCAGTCCTCA CTGATCACGT CAGACTCCAG GACCGAGAGC CACAATGCTT CAGGAAGCT	2943
2944	CAATGAA CCC AACAGCCACA TTTCCCTTC CTAAGCATAG ACA A GCA T TGGCAATAA	3273
3274	CCAAAAAAGAA TCCAGAGACT AAC T GGTGGT AGCTTTGCC TGGCA T CA AA A CTGGGCC GAAGTGA T AAC T G (PEA.1-Polyoma)	3333
3334	AGAGCAAGTG GAAAATGCCA GAGATTGTTA AACTTTCAC CCTGACCAAGC ACCCCACGCC	3393
3394	GCTCAGCAGT GACTGCTGAC ACCACGGAGT GACCTGCA G GCAGGGGAGG AGAAGA AAA C AGTCA G AGT GACCTG (ERE.2-Vitel.)	3453
3454	GAGAGGGATA GTGTATGAGC AAGAAAGACA GATTCA T CA AGGGCAGTGG GAATTGACCA	3513
3514	CGGGATTAT AGTCCACGTG ATCTGGTT CTAGGAGGCA GGGCTATATT GTGGGGGCAA (GRB-FLV) CGG G ATAC CGAGAGAAC A GGGCTATAGG	3573
3574	AAAATCAGTT CAAGGGAA G CGG G ACCT GATTTCTAAT ACTATA T TTT TCCTT T CA A GAGCC (SSRE)	3633
3634	GCTGAGTAAT TCTGAGCAAG TCA C AGGT A GTA A CTGAGG CTGTAAGATT ACTTAC T TC (ICS-MEII/ HLA-DR/1) AGT T TC	3693
3694	TCCTTATTAG GAACTCTTTT TCTCTGTGGA GTTACGAGCA CAAGGGCA T CCCGTTCTT TCCTCT	3753
3754	TTAACAGGAA GAAAAC T TC CTAAGAGTAA AGCC A ACAG ATTCA A GCCT AGGTCTTGCT	3813
3814	GA T ATATGAA TTGGTTTTT GAAAATCAT TTCAGGAGTG TT T ACTATGCT GATTCA G AA	3873

FIGURE 1C

3874	ATGAGACTAG TACCCTTTGG <u>TCA</u> GCTGTAA ACRAACACCC ATTTCATAAT GTCCTAAGTT CG TCA (1/2 SSRE)	3933
3934	CAGGCTTAAC TGCAGAACCA ATCAAATAAG AATAGAATCT TTAGAGCAA CTGTGTTCT	3993
3994	CCACTCTGGA GGTGAGTCTG CCAGGGCAGT TTGGAAATAT TTACTTCACA AGTATTGACA	4053
4054	CTGTTGTTGG TATTAACAAAC ATAAAGTTGC TCRAAGGCAA TCATTATTC AAGTGGCTTA	4113
4114	AAGTCACTTC TGACAGTTTT GGTATATTAA TTGGCAATG CCATTTGCTT TTTGTTTT (NF-1-HCMV) TTGGCAATG GCCA CTTT	4173
4174	CTCTTG GGGT TTATTAATGT AAAGCAGGGG TTTAACCT ACAGTCCAGA AAGCCTGTGA CTCTT (ISGF2)	4233
4234	ATTTGAATGA GGAAAAAAATT ACATTTTGT TTTTACCCAC TTCTAACTAA ATTCACATT (Zn binding) -----	4293
4294	TTATTCCATT GCGAATAGAG CCATAAATCT AAGTGTAA TACAGTACCC TGTGATTTC	4353
4354	TCATTACCA TAGAAATCAC AGACATTTA TACTATTTA CACTTGTGC AGATACGTTG (CAP-galO) ATTTA TTCCATGTC1 CACTTTGCC A	4413
4414	TAAGTGAAT ATTTATMTC AAAACTACTT TGAAATTAGA CCTCTGCTG GATCTTGT TAACTC A (AP-1)	4473
4474	TTAACATATT AATAAAACAT GTTAAATT TTGATTTTT GATAATCATA TTTCATTATC GAT GTTAAAT (PRL-FPII)	4533
4534	ATTTGTTCC TTTGTAATCT ATATTTTATA TATTTGAAA CATTTTCTG AGAAGAGTTC (GRE-MAREV) TGTTTTCTG AGAACATCAG	4593
4594	CCCAGATTTC ACCATGAGG TTCTTGGCAT Gcacacacac AGACTAGAA CTGATTAGA CCAGATCTC ACCATCATTAT (nGRE) CTCTGG CACACAC A (CREA) GGACAC AGAGTAGGG (AP-1-TGFD)	4653
4654	GGCTAACATT GACATTGGTG CCTGAGATGC AAGACTGAA TTAGAAAGTT CTCCCCAAGA (GC2) GATGCT GATGGATAAT TTAGAAGCTT CTCCCCACA	4713
4714	TACACAGTTG TTTTAAAGCT AGGGGTGAGG GGGGAATCT <u>GCCGCTTCTA TAGGAATGCT</u> (PEA-3) <u>AGGA</u> GGT	4773
4774	<u>CTCCCTGGAG CCTGGTAGGG TGCTGTCTT GGGTGCGC TGGCTCTTAT TTCTCTGT</u> CTC (SSRE) MIR Repeat Region	4833
4834	<u>CCCTGCTACG TCTTAAGGA CTGTTGGG TCTCTGTC CTAGCTAGT GCGTGGCACA</u> GGA CTTGGTTCT CT (GRE-PTAT-II) TGGGCACA GCAAAAGGA TCTATTGGA A (GRE-MMTV)	4893
4894	<u>GGCGAGTTTC TCAATGAGTT TGCAGAGTGA ATGGAAATAT AACATAGAAA TATATCGTG</u> GTGCCAA (NF-1) C TGTGAATCT TACCTAA	4953
4954	TTGAAATCAG CACACCAGTA GTCCTGGTGT AAGTGTGTGT ACGTGTGTGT GTGTGTGTGT	5013

FIGURE 1D

5014 GTGTGTGT AAAACCAGGT GGAGATATAG GAACTTTAT TGGGGTATGG GTGCATAAAT 5073
car/reverse car box

5074 TGGGATTC TTTTAAAA CGAACCTCA AGAACCTCTT GAAACTTAT TTTCTAAGAA 5133
(1/2 GRE) TGTC T (HSTP) GAAACTCTT GAAATATTCC CGAACCTTC
C CTTTAAAGAA GGA---CAA AGCGAATG (GRE-Pr1)

5134 TCTTGCTGGC AGCGTGAAGG CAAACCCCCCT GTGCGACGCC CCACCCAGEC TCTCGTGGCC 5193
(1/2 TRE) ACG CAA T-cc CGGGCTCCC -CAG (AP.2-SV40)
GGAGGCC CC (NF-κB)

5194 ACCTCTGTCT TCCCCCATGA AGGGCTGGCT CCCCATGATA TATAAACCTC TCTGGAGCTC 5253
tata box GGTC TC (SSRE)

5254 GGGCATGAGC CAGCGAAGGC 'C' ACCCATCCAG GCACCTCTCA GCACAGC 5300
Start Sites

FIGURE 1E

361 Leu Asn Thr Glu Thr Val Lys Ala Glu Lys Glu Ile Pro Gly Ala Gly Tyr His Gly Gln 380
381 Phe Pro Tyr Ser Trp Gly Gly Tyr Thr Asp Ile Asp Leu Ala Val Asp Glu Ala Gly Leu 400
401 Trp Val Ile Tyr Ser Thr Asp Glu Ala Lys Gly Ala Ile Val Leu Ser Lys Leu Asn Pro 420
421 Glu Asn Leu Glu Leu Glu Gln Thr Trp Glu Thr Asn Ile Arg Lys Gln Ser Val Ala Asn 440
441 Ala Phe Ile Ile Cys Gly Thr Leu Tyr Thr Val Ser Ser Tyr Thr Ser Ala Asp Ala Thr 460
461 Val Asn Phe Ala Tyr Asp Thr Gly Thr Gly Ile Ser Lys Thr Leu Thr Ile Pro Phe Lys 480
481 Asn Arg Tyr Lys Tyr Ser Ser Met Ile Asp Tyr Asn Pro Leu Glu Lys Lys Leu Phe Ala 500
501 Trp Asp Asn Leu Asn Met Val Thr Tyr Asp Ile Lys Leu Ser Lys Met

1261 GCG AAT CTG GAA CTC GAA CTA ACC TGG GAG AGA AAC ATC CGT AAG CGG TCA GTC GCC AAT 1320
1321 GCC TTC ATC ATC TGT GGC ACC TTG TAC ACC GTC AGC AGC TAC ACC TCA GCA GAT GCT ACC 1380
1381 GTC AAC TTT GCT TAT GAC ACA GGC ACA CGT ATC AGC AAG ACC CGG AGC ATC CCA TTC AAG 1440
1441 AAC CGC TAT AAG TAC AGC AGC ATG ATT GAC TAC AAC CCC CTG GAG AAG AAG CTC TTT GCC 1500
1501 TGG GAC AAC TTG AAC ATG GTC ACT TAT GAC ATC AAG CTC TCC AAG ATG 1548

1	ATC TTTGTCAGT TTACCTCAGG GCTATTATGA	33
34	AATGAAATGA GATAACCAAT GTGAAAGTC TATAAACTGT ATAGCCTCCA TTGGATGTA	93
94	TGCTTTGGC AGGATGATAA AGAACAGGA AGAAGGAGTA TCCACGTTAG CCAAGTGTC	153
154	AGGCTGTGTC TGCTCTTATT TTAGTGACAG ATGTTGCTCC TGACAGAAC TATTCTTCAG	213
214	GAAACATCAC ATCCAATATG GTAAATCCAT CAAACAGGAG CTAAGAAACA GGAAATGAGAT	273
274	GGGCCTTGC CCAAGGAAAA ATGCCAGGAG AGCATAATAT GATGAAAAAT AAACCTTTCC	333
334	CTTGTGTTT AATTTCAGGA AAAATGATG AGGACCAA TCAATGAATR AGGAAAACAG	393
394	CTCAGAAAAA AGATGTTCC AAATTGGTAA TTAAGTATTT GTTCCTTGGG ARGAGACCTC	453
454	CATGTGAGCT TGATGGAAA ATGGGAAAA CGTCAAAAGC ATGATCTGAT CAGATCCCRA	513
514	AGTGGATTAT TATTTAAAA ACCAGATGGC ATCACTCTGG GGAGGCAAGT TCAGGAAGGT	573
574	CATGTTAGCA AAGGACATAA CAAATAACAGC AAAATCAAAAT TTGGCGAAAT GCAGGAGGAA	633
634	AATGGGACT GGGAAAGCTT TCATAACAGT GATTAGGCAG TTGACCATGT TCGCCTACCC	693
694	TCCCCGTCTA TACCAGGGAA CACAAAAATT GACTGGGCTA AGCCTGGACT TTCAGGGAA	753
754	ATATGAAAAA CTGAGAGCAA AACAAAAGAC ATGGTTAAAA GGCCTACCGA ACATTGTGAG	813
814	CCTTCAAAGC AGCACTGCC CTCAGCAGGG ACCCTGAGGC ATTTCGCTTT AGGAAGGCCA	873
874	GTTTTCTTAA GGAATCTTAA GAAACTCTTG AAAGATCATG AATTTTAACC ATTTTAAGTA	933
934	TAACATCAAT ATGGATGCA TAATCAGTTT AGACATGGGT CCCATTCTTA TAAAGTCAGG	993
994	CATACAAAGGA TAACGTGTCC CAGCTCCGGA TAGGTCAAGAA ATCACTTAGAA ATCACTGTGT	1053
1054	CCCCATCTTA ACTTTTCAG AATGATCTGT CATAGCCCTC ACACACAGGC CCGATGTGTC	1113
1114	TGACCTACAA CCACATCTAC AACCCAAAGTG CCTCAACCAT TGTAAACGTG TCATCTCAGT	1173
1174	AGGTCCCTT ACAAATGCCA CCTCCCCCTGT CGAGCCCATC CGGCTCACA GGAAGTCTCC	1233
1234	CCACTCTAGA CTTCTGCATC ACGATGTTAC AGCCAGAAC TCCGTGAGGG TGAGGGTCTG	1293
1294	TGTCTTACAC CTACCTGTAT GCTCTACACC TGAGCTCAGT GCACCTCTG CCTCCAGGT	1353
1354	TCAAGCAATT CTCCTGTCTC AGCCTCCCGC GTAGCTGGGA CTACRGCGC ACCCCCCGGCT	1413
1414	AATTTTGTA TTGTTAGTAG AGATGGGTT TCACCATATT AGCCCGGCTG GTCTTGAACT	1473

FIGURE 2A

1474	CCTGACCTCA GGTGATCCAC CCACCTCGC CTCTAAAGT GCTGGGATTA CAGGCATGAG	1533
1534	TCAACGGCGCC CGGCCAAGGG TCACTGTTA ATAAGGAATA ACTTGAAATGG TTTACTAAAC	1593
1594	CAACAGGGAA ACAGACAAAA GCTGTGATAA TTTCAGGGAT TCTTGGGATG GGGAAATGGTG	1653
1654	CCATGAGCTG CCTGCCTAGT CCCAGACCAC TGGTCCTCAT CACTTTCTTC CCTCATCCTC	1713
1714	ATTTTCAGGC TAAGTTACCA TTTTATTACAC CATGCTTTTG TGGTAAGCCT CCACATCGTT	1773
1774	ACTGAAATAA GAGTATAACAT AAACTAGTTC CATTTCGGGC CATCTGTGTTG TGTGTATAGG	1833
1834	GGAGGAGGGC ATACCCCAGA GACTCCTTGA AGCCCCCGGC AGAGGTTTCC TCTCCAGCTG	1893
1894	GGGGAGCCCT GCAAGCCTCCC GGGGTCTGG GTGTCTGAG CAACCTGCCA GCGCGTGCCT	1953
1954	CTGGTTGTTT TGTTATCCT CTCTAGGGAC CTGGTTGCTTT CTATTTCTGT GTGACTCGTT	2013
2014	CATTCCATCCA GGCATTCATT GACATTATAT TGAGTACTTA TATCTGCCAG ACACCGAGA	2073
2074	CAAAATGGTG AGCAAAGCAG TCACCTGCCCT ACCTTCGTGG AGGTGACAGT TTCTCATGGA	2133
2134	AGACGTGCAG AAGAAAATTA ATAGCCAGCC AACTTAAACC CAGTGCTGAA AGAAAGGAAA	2193
2194	TAAACACCAT CTTGAAGCAT TGTGGCGAGC ATCCCTTAAC AAGGCCACCT CCCTAGCGCC	2253
2254	CCCTGCTGCC TCCATCGTGC CCGGAGGCC CCAAGCCCA GTCTTCCAAG CCTCTCTCTC	2313
2314	CATCAGTCAC AGCGCTCCAG CTGGCCTGCC TCGCTTCCCG TGAATCGTCC TGGTGCATCT	2373
2374	GAGCTGGAGA CTCCTGGCT CCAGGCTCCA GAAAGGAAAT GGAGAGGGAA ACTAGTCTAA	2433
2434	CGGAGAATCT GGAGGGGACA GTGTTTCTC AGAGGGAAAG GGGCCTCAC GTCCAGGAGA	2493
2494	ATTCCAGGAG GTGGGGACTG CAGGGAGTGG GGACGCTGGG GCTGAGGGGG TGCTGAAAGG	2553
2554	CAGGAAGGTG AAAAGGCCAA GGCTGAAGCT GCCCAGATGT TCAGTGTGTT TCACGGGGCT	2613
2614	GGGAGTTTTC CGTTGCTTCC TGTGAGCCCTT TTTATCTTTT CTCTGCTTGG AGGAGAAGAA	2673
2674	GTCTATTTCA TGAAGGGATG CAGTTTCATA AAGTCAGCTG TTAAAATTCG AGGGTGTGCA	2733
2734	TGGGTTTCC TTCACGAAGG CCTTTATTTA ATGGGAATAT AGGAACCGAG CTCATTCCT	2793
2794	AGGCCGTTAA TTCACGGAAAG AAGTGACTGG AGTCTTTCTT TTCACTGCTT CTGGGCAACT	2853
2854	ACTCAGCCCT GTGGTGGACT TGGCTTATGC AAGACGGTCG AAAACCTTGG AATCAGGAGA	2913
2914	CTCGGTTTTC TTTCTGGTTTC TGCCATTGGT TGGCTGTGCC ACCGTGGCA AGTGTCTCTC	2973
2974	CTTCCCTGGG CCATAGTCTT CTCTGCTATA AAGACCCCTG CAGCTCTCGT GTTCTGTGAA	3033
3034	CACTTCCCTG TGATTCTCTG TGAGGGGGAA TGTTGAGAGG GGAAACGGGC AGACCTGGAG	3093

FIGURE 2B

3094	CAGCTGAGCC ACAGGGGAGG TGGAGGGGGA CAGGAAGGC A GCGAGAAGCT GGGTGCTCCA	3153
3154	TCACTCCTCA CTGATCAGT CAGACTCCAG GACCGAGAGC CACAATGCTT CAGGAAAGCT	2943
2944	CAATGAACCC AACAGCCACA TTTTCCTTCC CTAAGCATAG ACAATGGCAT TTGCCAATAA	3273
3274	CCAAAAAGAA TGCAGAGACT AACTGGTGGT AGCTTTGCC TGGCATTCAA AAACCTGGGCC	3333
3334	AGAGCAAGTG GAAAATGCCA GAGATTGTTA AACTTTCAC CCTGACCRGC ACCCCACGCC	3393
3394	GCTCAGGAGT GACTGCTGAC AGCACGGAGT GACCTGCAGC GCAGGGGAGG AGAAGAAAAA	3453
3454	GAGAGGATA GTGTATGAGC AAGAAAGACA GATTCATTCA AGGGCAGTGG GAATTGACCA	3513
3514	CAGGGATTAT AGTCCACGTG ATCCTGGGTT CTAGGAGGCA GGGCTATATT GTGGGGGAA	3573
3574	AAAATCAGTT CAAGGGAAAGT CGGGAGACCT GATTTCTAAT ACTATATTTT TCCTTTACAA	3633
3634	GCTGAGTAAT TCTGAGCAAG TCACAAAGGTAA GTAACTGAGG CTGTAAGATT ACTTAGTTTC	3693
3694	TCCTTATTAG GAACTCTTTT TCTCTGTGGA GTTAGCAGCA CAGGGCAAT CCCGTTTCTT	3753
3754	TTAACAGGAA GAAAACATTC CTAAGAGTAA AGCCAAACAG ATTCAAGCCT AGGTCTTGCT	3813
3814	GAECTATATGA TTGGTTTTTTT GAAAAATCAT TTCAAGCGATG TTTACTATCT GATTAGAAA	3873
3874	ATGAGACTAG TACCCCTTGG TCAGCTGTAA ACAAAACACCC ATTTGTAAAT GTCTCAAGTT	3933
3934	CAGGCTTAAC TGCAGAACCA ATCAAATAG AATAGAATCT TTAGAGCRAA CTGTGTTCT	3993
3994	CCACTCTGGA GGTGAGTCTG CCAGGGCAAGT TTGGAAATAT TTACTTCACA AGTATTGACA	4053
4054	CTGTTGTGG TATTAACAAC ATAAAGTTGC TCAAAGGCAA TCATTATTC AAGTGGCTTA	4113
4114	AAGTTACTTC TGACAGTTTT GGTATATTAA TTGGCTATTG CCATTTGCTT TTTGTTTTTT	4173
4174	CTCTTGGGT TTATTAATGT AAAGCAGGGA TTATTAACCT ACAGTCCAGA AAGCCTGTGA	4233
4234	ATTTGAATGA GGAAAAAATT ACGTTTTTAT TTTTACCAACC TTCTAACTAA ATTTAACATT	4293
4294	TTATTCCATT GCGAAATAGAG CCATAAAACTC AAAGTGGTAA TAAGAGTACC TGTGATTTC	4353
4354	TCATTACCAA TAGAAATCAC AGACATTAA TACTATATTA CAGTTGTGTC AGGTACGTTG	4413
4414	TAAGTGAATAT ATTTATRACTC AAAACTACTT TGAAATTAGA CCTCCTGTG GATCTTGTAA	4473
4474	TTAACATATT AATAAAACAT GTTTAAAATT TTGATATTTT GATAATCATA TTTCATTATC	4533
4534	ATTTGTTTCC TTTGTAATCT ATATTTATA TATTGAAAA CATCTTTCTG AGAAGACTTC	4593
4594	CCCAGATTTC ACCAATGAGG TTCTTGGCAT GCGCAGCACAC AGAGTAAGAA CTGATTAGA	4653
4654	GGCTAAGATT GACATTGGTG CCTGAGATGC AACAGTGAAT TTAGAATGTT CTCCCAAGA	4713

FIGURE 2C